Novel Transition-Metal-Catalysed Reactions using Diethylzinc as the Stoichiometric Reductant

Thesis Submitted in Accordance with the Requirements of the University of Edinburgh for the Degree of Doctor of Philosophy

By

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Abstract

Modern organic chemistry strives to achieve rapid molecular complexity from simple achiral substrates. One method by which this may be achieved is with enolate formation followed by attack on an electrophile which can generate one, two or even more new stereocentres in one step. However regioselective generation of an enolate in the presence of several enolisable sites has always proved problematical. A partial answer to this problem has been provided by the development of the reductive aldol reaction.

The first part of this thesis is concerned with describing a highly diastereoselective Co(II)-catalysed reductive aldol reaction between α,β-unsaturated amides and ketones. The reaction proceeds using substoichiometric quantities of cobalt(II) in the presence of a stoichiometric quantity of the reductant diethylzinc. Using both *N,N*-dimethyl and morpholine amides, the reactions are tolerant of substituted aromatic ketones as well as aliphatic ketones. The reaction also proceeded well when the β-carbon was substituted with both aromatic and aliphatic groups resulting in improved diastereoselection.

The racemic work is followed by the development of an asymmetric version of the reaction using oxazolidinone chiral auxiliaries that impart high levels of diastereofacial selectivity. The reaction was found to proceed with a variety of aromatic ketones and once again, substitution of the β-carbon resulted in improved diastereoselectivity.

Finally work on formal homo aldol cyclisations using substoichiometric quantities of Ni(II) also in the presence of a stoichiometric quantity of diethylzinc is described. This work aims to develop methodology that involves double cyclisations with the formation of up to five contiguous stereocentres. Although unsuccessful, useful conclusions for future work were made as well as the serendipitous discovery of a apparent base catalysed alternative cyclisation pathway that successfully generated two new rings and four contiguous stereocentres.

Acknowledgments

This thesis is the result of three years work in which I have had the privilege of living and working with many very kind and interesting people. First, I would like to thank my supervisor Dr Hon Wai Lam for giving me the opportunity to engage in what has been a very enjoyable PhD experience. Hon was always available when I had a problem, always interested in what I had to say and for three years, made sure the work stayed on track.

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Last of all I would like to thank my mum, Jacky for continual support and advice, to my dad, David also for support and advice and also for trying to read this thesis, and to my sister, Esther for taking an interest in what I have done and for picking out all the occurrences where the ‘ester’ functional group is written.

Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained in this thesis is the original work of my own research since the registration of the PhD degree in September 2005, and any collaboration has been clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

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Ralph James Richard Lumby

January 2008

Contents:

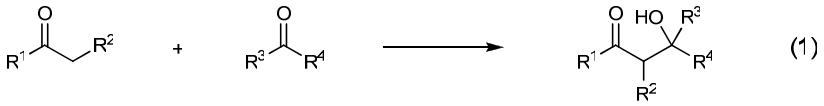
List of Abbreviations

acac	acetylacetonate
aq	aqueous
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Brine	saturated aqueous sodium chloride solution
Cat	catalyst
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
cod	cyclooctadiene
DCE	dichloroethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
duphos	1,2-bis(2,5)-diethylphospholano benzene
ee	enantiomeric excess
EtOAc	ethyl acetate
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high-performance liquid chromatography
h	hours
IR	infrared spectroscopy
min	minutes
MS	molecular sieves
NCS	*N*-chlorosuccinimide

PG	protecting group
PMP	4-methoxyphenyl
RT	room temperature
segphos	5,5’-bis(diphenylphosphino)-4,4’-bi-1,3-benzodioxole
TBDMS	tributyldimethylsiloxane
OTf	oxygentrifluoromethansulfonate
THF	tetrahydrofuran
TMDS	tetramethyldisiloxane
TMS	trimethylsilyl

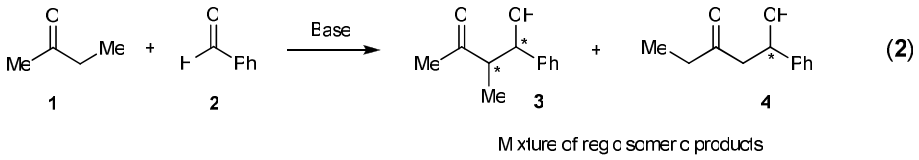
1 Introduction to the Reductive Aldol Reaction

Enolates are one of the most important classes of carbon nucleophile in organic chemistry and are used in several classical transformations including the aldol reaction.[1] The aldol reaction involves the addition of the α-carbon of an enolisable carbonyl species to an aldehyde or ketone, generating a β-hydroxycarbonyl moiety (Eq 1).



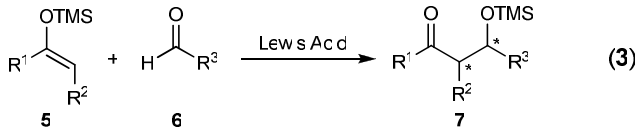
(1)

Although the aldol reaction has been known for over 100 years,[2] control over regioselectivity in the reaction remains a key limiting factor due to the problem of multiple enolisable sites (Eq 2).



(2)

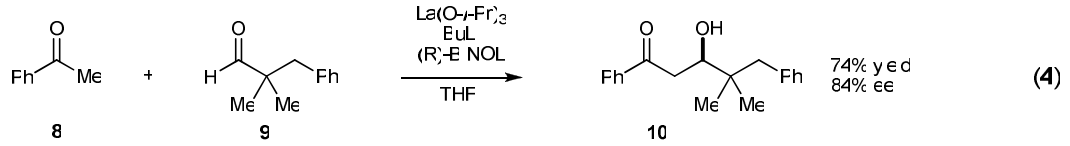
Ideally, a molecule possessing multiple enolisable sites (for example ketone **1**), should be subject to chemo- and regioselective formation of the enolate. In reality, this is rarely the case so the reactants have to be modified as a solution to competitive enolate formation. The most common of these modified reagents are the silyl enol ethers (**5**) used in the Mukaiyama aldol reaction,[3] which is subsequently coupled with an aldehyde or ketone (Eq 3).

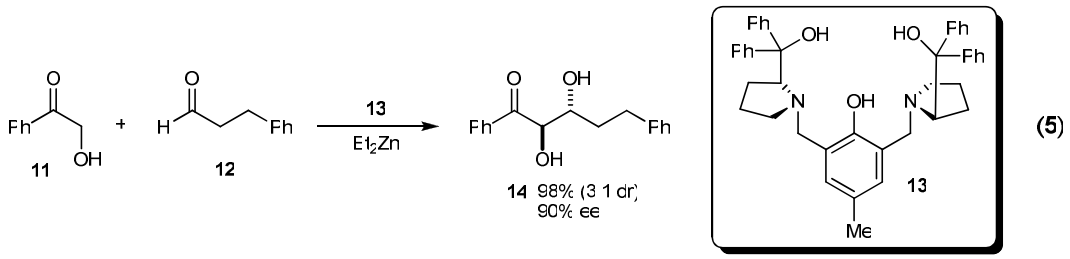


(3)

Although effective, this methodology does have its limitations, since it requires the pre-formation of highly reactive and relatively unstable intermediates which must be used immediately once synthesised.

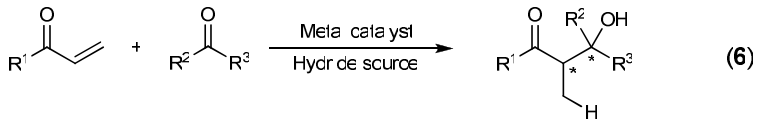
There are some examples of methodologies that achieve enantioselective catalytic direct aldol condensations with the use of unmodified ketones as pronucleophiles.[4] In these reactions, ketones possessing only one enolisable site (Eq 4)[5] or ketones where enolate formation is directed by an α-hydroxy group (Eq 5)[6] were utilised.





Even though this progress is undeniably significant, it does not solve the problem of regioselectivity for the majority of reactants as it is limited to a narrow scope of substrate that fit the necessary criteria.

Another major contribution to the problem of multiple enolisable sites has been found in the reductive aldol reaction which is the direct reductive addition of α,β-unsaturated carbonyl compounds to an acceptor aldehyde or ketone. The reaction is performed in the presence of a metal promoter (usually a catalytic quantity) and a stoichiometric amount of a reducing agent (Eq 6).



The reductive aldol reaction allows the mild and regioselective formation of the desired enolate in the presence of other carbonyl species using commercially available materials with no pre-formation of an enolate required. In addition, the β-hydroxy carbonyl products can be isolated either as the free hydroxyl compound or as the silyl ether if silanes are used as the reducing agent. However, the reaction is not without its limitations and still poses significant challenges. The electrophilic

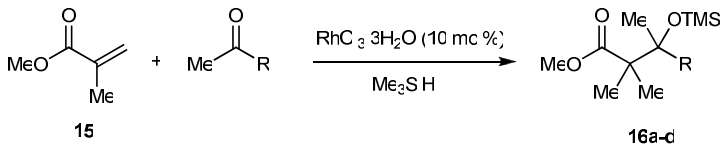
carbonyl has to be inert toward reductive conditions. In addition, metathesis between the hydride source and the metal enolate must be slower than the carbon-carbon bond-forming aldol reaction.

In the following section, the major developments in the field of reductive aldol chemistry will be highlighted. The reaction has been mediated by many different metals and so each one will be presented in turn.

1.1 Rhodium-Catalysed Reductive Aldol Reactions

1.1.1 Hydrosilane-Mediated Reactions

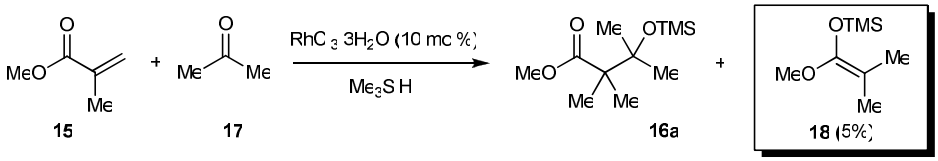
The first example of a reductive aldol reaction was reported by Revis and Hilty in 1987.[7] Methyl methacrylate (1 equiv) was reacted with a range of ketones and aldehydes (excess) in the presence of a substoichiometric amount of $RhCl_3 \cdot 3H_2O$ (9 mol%) along with trimethylsilane (1.3 equiv) as the hydride source (Eq 7).



Product	R	Yield (%)
16a	Me	95
16b	Et	91
16c	H	78
16d	OEt	NR

(7)

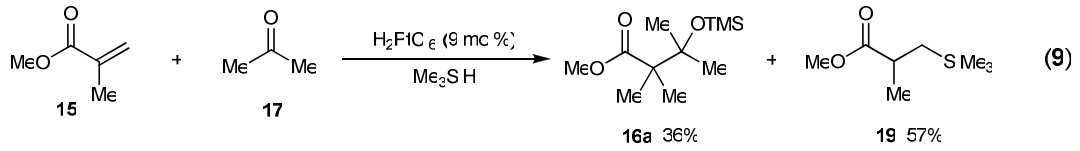
In the course of this pioneering work, silyl ketene acetal **18** was also isolated in 5% yield (Eq 8).



(8)

Revis and Hilty initially postulated that the formation of aldol product **16a** proceeded through ketene acetal **18** in a Mukaiyama type coupling (Eq 3). To test this

hypothesis, **18** was independently synthesised and subjected to the reaction conditions. Surprisingly, only 2% of the aldol product **16a** formed. Further evidence was gained when the same reaction was performed using Spiers catalyst (H_2PtCl_6) (Eq 9).

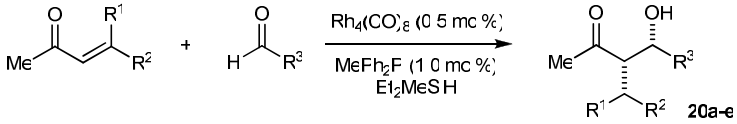


(9)

Only two main products formed, aldol adduct **16a** (36%), and silane **19** (57%) and none of the ketene acetal **18** was observed. In the absence of acetone, H_2PtCl_6 produced only **19** which strongly suggested the reaction does not proceed via a silyl ketene acetal. Based on these facts, Revis concluded that the reaction was proceeding through a new and unknown reaction pathway. Although this 'hydrosilylative condensation' is limited to the use of esters as pro-nucleophiles, both ketones and aldehydes can be used as the electrophile under these conditions without any major 1,2 or 1,4 conjugate reduction side products.

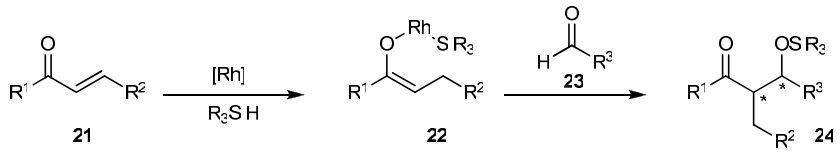
In 1990, Matsuda and co-workers were the first to report diastereoselective rhodium catalysed reductive aldol reactions between α,β-unsaturated ketones and aldehydes using trialkylsilanes as a hydride source.[8] A very low catalyst loading of $Rh_4(CO)_{12}$ (0.5 mol%) with PPh_2Me as ligand was used to effect reaction between methyl vinyl ketone and benzaldehyde providing reductive aldol product **20a** in near quantative yield (Table 1, entry 1). Reactions were also performed with aliphatic ketones (entries 2 and 3) although these reactions proved to be lower yielding and less selective. Extension of the methodology to include substituted methyl vinyl ketones provided aldol products in good yield but with modest diastereoselectivity (entries 4 and 5).

Table 1: Representative Selection of Reactions Between α,β-Unsaturated Ketones and Aldehydes



Entry	R^1	R^2	R^3	Product (Yield %)	dr (*Syn:anti*)
1	H	H	Ph	**20a** (99%)	83:17
2	H	H	$(CH_2)_6CH_3$	**20b** (80%)	68:32
3	H	H	*c*-C_6H_{11}	**20c** (63%)	58:42
4	H	Ph	Ph	**20d** (88%)	55:45
5	Me	Me	Ph	**20e** (86%)	80:20

Like Revis, Matsuda synthesised silylketene acetals and demonstrated that they were unreactive under the reaction conditions. Using mechanistic information discovered by Bergman and Heathcock in 1989,[9] Matsuda proposed a tentative mechanism for the rhodium catalysed reductive aldol reaction, suggesting that an oxygen-bound rhodium enolate **22** reacted directly with the aldehyde electrophile **23** (Eq 10).

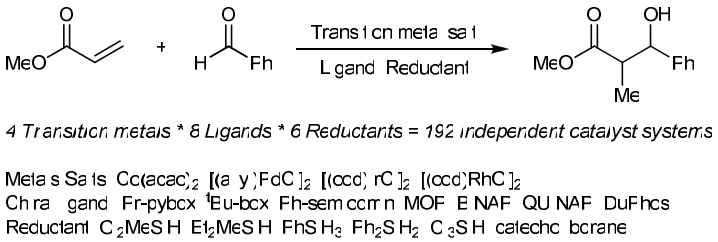


(10)

Initially, the reaction worked well using benzaldehyde as an electrophile but when the reaction was attempted with enolisable aldehydes, the reaction did not produce acceptable results. This problem was overcome by modification of the $Rh_4(CO)_{12}$ catalyst with $MePh_2P$. In addition, the problem of side-product formation was reduced by conducting the reactions at 0 ^oC.

By this stage, reductive aldol reactions were producing products in good yields but with modest levels of diastereoselectivity. Since at this time, little was known about the reaction mechanism, it was difficult to determine the most important factors in

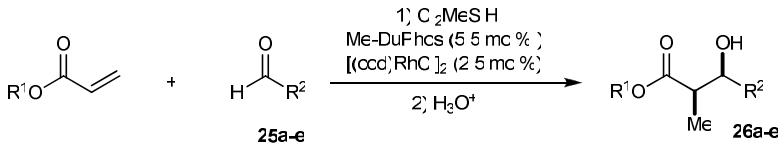
terms of improving diastereoselection. Morken and co-workers believed that the best way to tackle this problem was to conduct an arrayed catalyst evaluation using 96-well plates.[10] The initial array used four transition metals, seven ligands (plus one blank), and six hydride sources. A model transformation between methyl acrylate and benzaldehyde was chosen (Scheme 1).

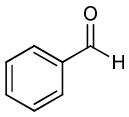
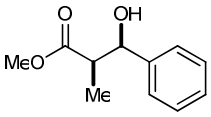
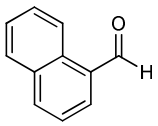
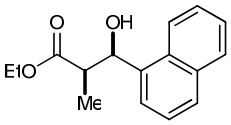
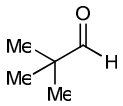
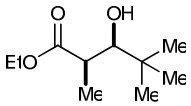
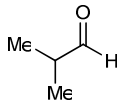
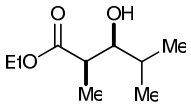
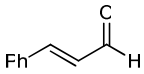
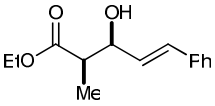


Scheme 1: Parameters for Arrayed Catalyst Screen

Analysis of the results identified $[(cod)RhCl]_2$, DuPhos, and Cl_2MeSiH (94% yield, 23:1 (*syn:anti*) selectivity, athough with no ee) as the most promising combination and so these conditions were used with a range of aldehydes (Table 2).

Table 2: Catalytic Stereoselective Reductive Aldol Reactions with Ketones

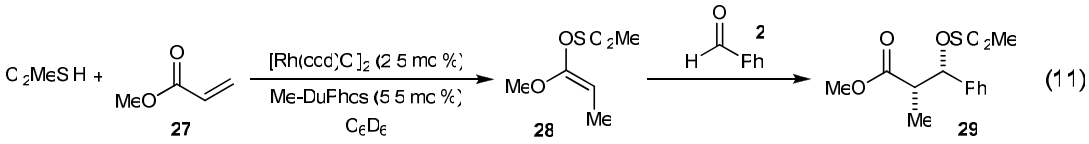


Entry	RCHO	Product	Yield (%)	d.r. (*syn:anti*)
1	 **25a**	 **26a**	69	23:1
2	 **25b**	 **26b**	82	10:1
3	 **25c**	 **26c**	38	21:1
4	 **25d**	 **26d**	15	15:1
5	 **25e**	 **26e**	41	>20:1

Repeating the model reaction between methyl acrylate and benzaldehyde on a preparative scale reaction (entry 1) afforded the desired aldol product in 69% yield with 23:1 (*syn:anti*) selectivity. Aromatic aldehydes gave moderate yields with high levels of diastereoselectivity (entries 1-2) while aliphatic aldehydes were formed in disappointingly low yields, though high levels of stereoselectivity were maintained (entries 3-4). Two points are worth noting; the first is that unsaturated aldehydes can participate in the reaction without interference from competitive conjugate reduction

(entry 5). The second is that no enantioselection was observed for any of the reactions in which chiral ligands were used.

In effort to understand the reaction pathway and hence explain the total lack of enantioselectivity, Morken next decided to conduct a range of ^{1}H NMR spectroscopic experiments.[11] Initially, the Rh-DuPhos-catalysed reaction between methyl acrylate (**27**) and Cl_2MeSiH was monitored by ^{1}H NMR spectroscopy (Eq 11). After approximately 1 hour, the reagents were completely converted into a single diastereoisomer of the derived silyl ketene acetal **28**. Subsequent introduction of benzaldehyde (**2**) led to the rapid consumption of this intermediate to afford a single diastereomer of the reductive aldol adduct **29**.



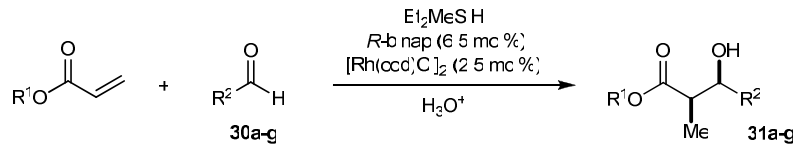
(11)

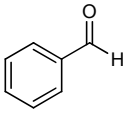
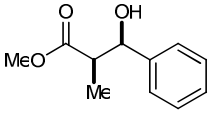
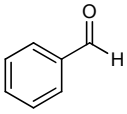
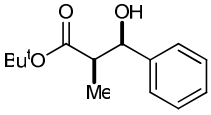
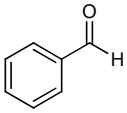
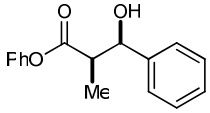
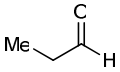
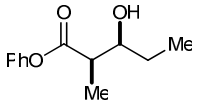
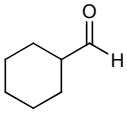
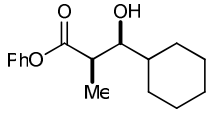
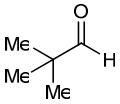
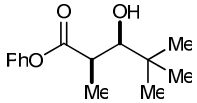
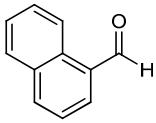
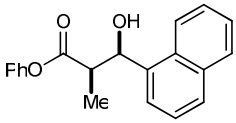
Next, Morken wanted to determine whether the Rh-DuPhos catalyst was required for reaction between the silyl ketene acetal and the aldehyde. A second experiment was conducted where the silyl ketene acetal was vacuum-distilled to separate it from the metal complex. Addition of benzaldehyde to the metal-free and phosphine-free silyl ketene acetal provided the aldol adduct with high diastereoselectivity. These observations showed that the Rh-DuPhos catalyst was not involved in the aldol addition step and hence no enantioselectivity was possible. It is of note however, that this two-step method dramatically increased both yield and diastereoselectivity when compared to the previously mentioned one step method.

Morken and co-workers were also the first to develop an asymmetric catalytic reductive aldol reaction.[12] During the initial catalyst screening process (Scheme 1), it was observed that the use of $[(cod)RhCl]_2$, (*R*)-binap and Et_2MeSiH resulted in 20% enantiomeric excess. It was postulated that in the high-throughput catalyst screening, complexation of the ligand to the metal was inefficient and so the metal salt alone was catalysing some of the reaction, resulting in less selectivity. To solve this

problem, excess ligand with respect to the metal salt was employed. The increased complexation resulted in higher enantioselectivity up to a maximum of 99% (Table 3, entry 1), although diastereoselectivity was greatly reduced (Table 3, entries 1-7).

Table 3: Rh-Catalysed Asymmetric Reductive Aldol Reactions With Aldehydes



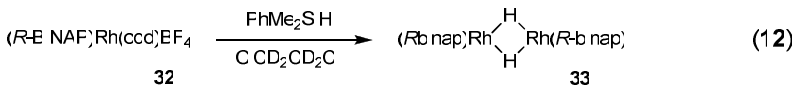
Entry	RCHO	Product	Yield (%)	d.r. (*syn:anti*)	ee (%) (*syn:anti*)
1	 **30a**	 **31a**	37	1.7:1	91 (88)
2	 **30b**	 **31b**	21	1.4:1	58 (38)
3	 **30c**	 **31c**	72	3.4:1	87 (34)
4	 **30d**	 **31d**	59	5.1:1	88 (7)
5	 **30e**	 **31e**	54	3.9:1	84 (48)
6	 **30f**	 **31f**	48	1.8:1	45 (>99)
7	 **30g**	 **31g**	82	3.8:1	80 (13)

The reductive aldol reaction between acrylate esters and aldehydes proceeded to generate aldol products with impressive levels of enantioselection using both aromatic and aliphatic aldehydes. However, whilst reaction with methyl acrylate

proceeded in high enantiopurity, the product was isolated in low yield (entry 1). Reaction with t-butyl acrylate exhibited both a diminished level of stereoselection and a very low yield (entry 2). Electronic effects in the acrylate component appear to be important since when phenyl acrylate was used, both high yield and high enantiomeric excesses were obtained along with slightly improved diastereoselectivity (entry 3). Using phenyl acrylate, a range of both aromatic and aliphatic aldehydes were tested. Generally good stereoselectivity was observed along with moderate to good yields (entries 4-7).

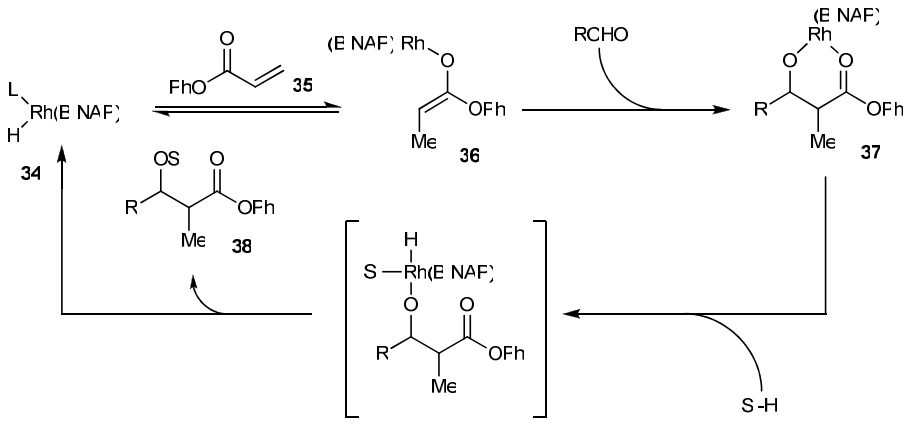
Since the new $[(cod)RhCl]_2$-(*R*)-BINAP-Et_2MeSiH system was enantioselective, it was assumed the mechanism did not proceed via a silyl ketene acetal as had been the case with the earlier $[(cod)RhCl]_2$-Me-Duphos-Et_2MeSiH catalyst system. Therefore Morken and co-workers undertook further study in order to better understand this new mechanism.[13]

(*R*-BINAP)Rh(cod)BF_4 was used as the transition metal catalyst and was subjected to each of the reaction components (acrylate, aldehyde, and silane). When the acrylate and aldehyde were added no reaction was observed. However, addition of $PhMe_2SiH$ provided a Rh(I) hydride dimer **33** as well as cyclooctadiene. ^{19}F NMR spectroscopy also indicated the presence of $PhMe_2SiF$ (Eq 12).



(12)

Based on these observations, Morken proposed the mechanism that is shown below (Scheme 2). Dissociation of the bridged dimer **33** provides a Rh(I) hydride **34** that can react with the acrylate **35** in a hydrometallation reaction to form a Rh(I) enolate **36**. This enolate then participates in an aldol addition step with the aldehyde to form an aldolate **37**. Oxidative addition of silane followed by reductive elimination of the silylated product **38** regenerates the active Rh(I) species **34** to complete the catalytic cycle.



Scheme 2: Proposed Mechanism for the Rhodium-Catalysed Reductive Aldol Reaction

More recently, Nishiyama and co-workers reported a series of reductive aldol reactions using Rh(Phebox) catalysts and silanes coupling t-butyl acrylate with aldehydes.[14] From an initial screen, two Rh(Phebox) catalysts in particular displayed exceptional relative and absolute stereochemical control (Figure 1).

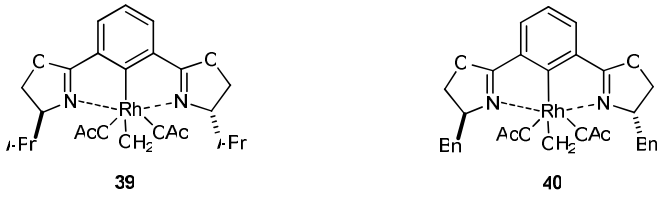
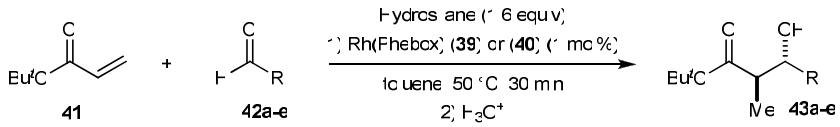
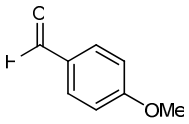
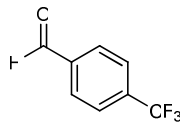
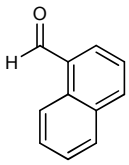
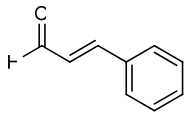
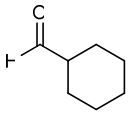


Figure 1: Chiral Rh(Phebox) Complexes

Using the optimised conditions, reactions were performed between t-butyl acrylate (**41**) and different aldehydes (**42a-e**) using the most appropriate silane and catalyst for each aldehyde (Table 4).

Table 4: Rh(Phebox)-Catalysed Intermolecular Reductive Aldol Reaction Between t-Butyl Acrylate and Benzaldehyde



Entry	RCHO	Silane	Yield % (Product)	d.r. (anti:syn)	ee (%) anti (syn)
1	 **42a**	$(EtO)_2MeSiH$	98 (**43a**)	94:6	94 (42)
2	 **42b**	Me_2PhSiH	95 (**43b**)	87:13	93 (27)
3	 **42c**	$(EtO)_2MeSiH$	97 (**43c**)	98:2	99 (-)
4	 **42d**	$(EtO)_2MeSiH$	56 (**43d**)	81:19	93 (79)
5	 **42e**	$(EtO)_2MeSiH$	72 (**43e**)	86:14	93 (57)

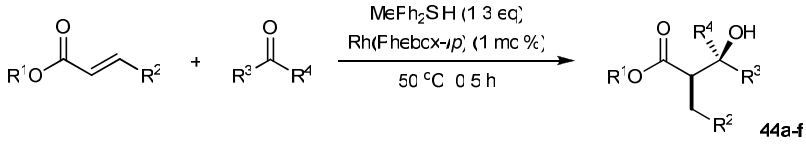
The reaction tolerates electron-withdrawing and donating groups on the aromatic ring of the aldehyde (entries 1-2) as well as more sterically challenging substrates (entry 3) and saturated aldehydes (entry 5). All the products were obtained with good diastereoselectivity and excellent enantioselectivity. Unusually for this type of reaction, the diastereoselectivity is anti-selective in contrast to earlier work by

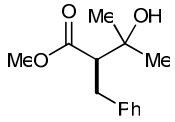
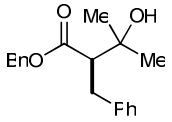
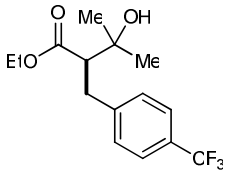
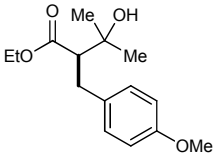
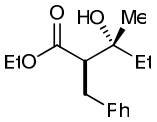
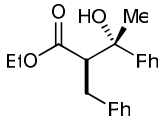
Morken. It was also found that catalyst loading could be reduced to as low as 0.1 mol% and the catalyst could be recovered as the chloride complex.

In order to help clarify the reaction mechanism, reactions were performed in the absence of benzaldehyde. After 1 hour, a mixture of the corresponding *E:Z* (95:5) silylketene acetal was observed, however no aldol product was observed on the addition of benzaldehyde. This led to the conclusion that the reaction proceeds via a Rh-enolate complex similar to that previously reported by Morken and co-workers.

As an extension of their earlier work, Nishiyama and co-workers reported an asymmetric reductive aldol reaction between cinnamates or crotonate substrates and ketones using a Rh(Phebox-ip) catalyst and $MePh_2SiH$ as a hydride source (Table 5).[15]

Table 5: Asymmetric Reductive Aldol Reactions Between α,β-Unsaturated Esters and Ketones

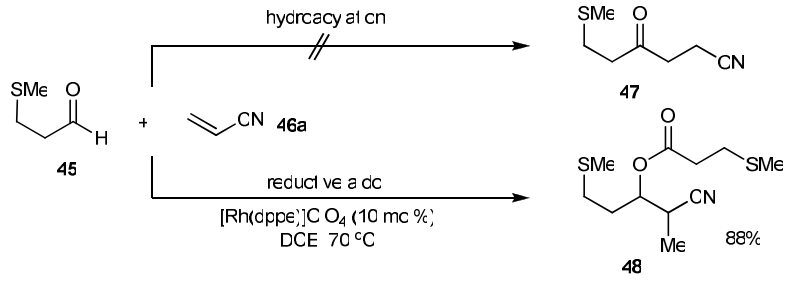


Entry	R^1	R^2	Ketone	Product	Yield	d.r. (%)	ee (%)
1	Me	Ph	Acetone	 **44a**	83	-	96
2	Bn	Ph	Acetone	 **44b**	82	-	96
3	Et	4-CF_3Ph	Acetone	 **44c**	64	-	97
4	Et	4-OMePh	Acetone	 **44d**	81	-	96
5	Et	Ph	MeCOEt	 **44e**	66	59:41	96/96
6	Et	Ph	MeCOPh	 **44f**	90	96:4	97/38

Reactions were performed with a range of substrates and high to moderate yields were obtained in excellent enantiomeric excess. Methyl and benzyl cinnamates gave almost identical results (entries 1-2). The presence of the electron withdrawing *p*-CF_3 resulted in reduced yield compared to the electron donating *p*-MeO, however levels

of enantiomeric excess were unaffected (entries 3-4). Only two reactions were performed using an unsymmetrical ketone, resulting in the formation of two new stereocentres (entries 5-6). Again, enantiomeric excess was high in both cases with good diastereocontrol in the case of acetophenone, and poor diastereocontrol with butanone.

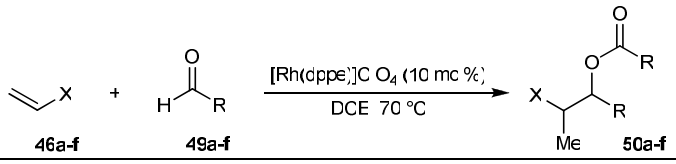
In 2005, Willis and Woodward reported a novel reductive aldol reaction between α,β-unsaturated nitriles and aldehydes.[16] This work stemmed from the unexpected products obtained during a reaction between β-methyl sulphide-substituted propanal **45** and acrylonitrile (**46a**) (Scheme 3).



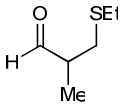
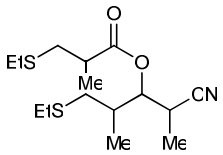
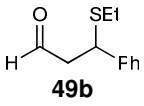
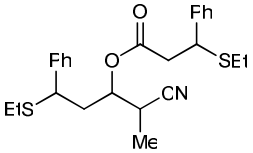
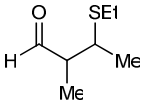
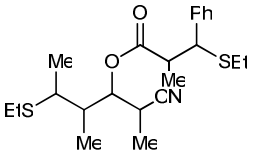
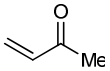
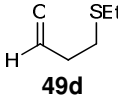
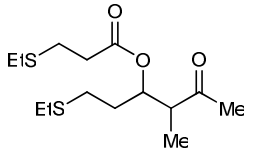
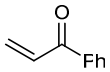
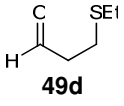
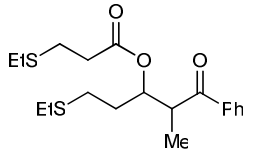
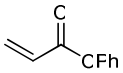
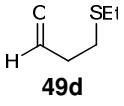
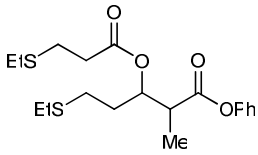
Scheme 3: A New Type of Reductive Aldol Reaction Between Acrylonitrile and Aldehyde 45

Using [Rh(dppe)]ClO_4 as the catalyst, attempts to produce the desired product **47** failed, however ester **48** was obtained in good yield. The scope of the reaction was now extended to include reactions with α,β-unsaturated ketones and esters as well as varying the aldehyde substrate (Table 6).

Table 6: Reductive Aldol Reaction Using Aldehydes as the Stoichiometric Reductants

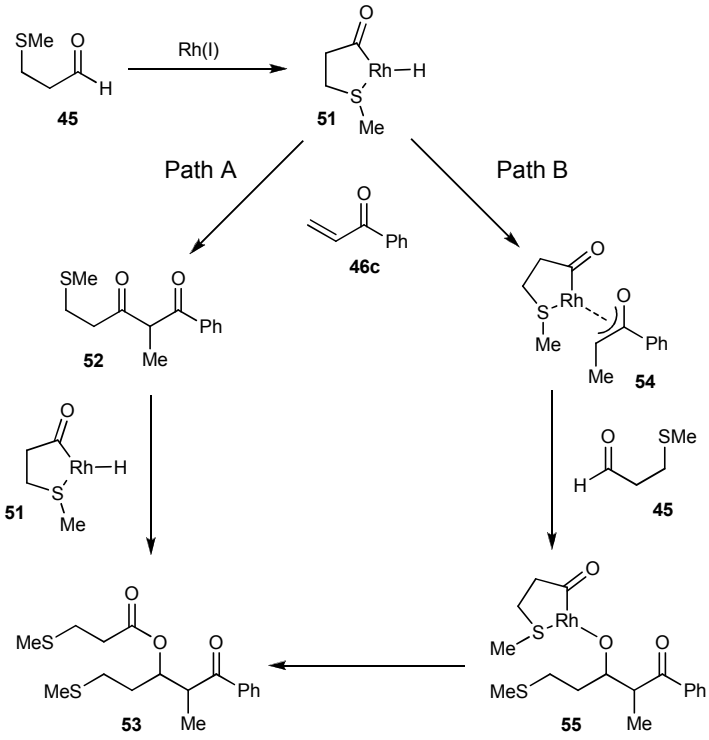


46a-f 49a-f 50a-f

Entry	Alkene	Aldehyde	Product	d.r.	Yield (%)
1	 **46a**	 **49a**	 **50a**	6.6:3.6:1	88
2	 **46a**	 **49b**	 **50b**	1.1:1	71
3	 **46a**	 **49c**	 **50c**	1.4:1	93
4	 **46b**	 **49d**	 **50d**	7.5:5:1	73
5	 **46c**	 **49d**	 **50e**	3.3:1	74
6	 **46d**	 **49d**	 **50f**	3.3:1	67

Reactions of acrylonitrile with various aldehydes resulted in the formation of the desired products in good to moderate yields with α- or β-methyl or β-phenyl substitution well tolerated (entries 1-3). In addition, methyl- and phenyl vinyl ketones (entries 4-5) as well as phenyl acrylate (entry 6) partook in the reaction in good yield. However, the reaction does suffer from generally low diastereoselectivity and the mixture of diastereomers obtained were inseparable by column

chromatography. Willis proposed two possible mechanisms for this new reaction (Scheme 4).

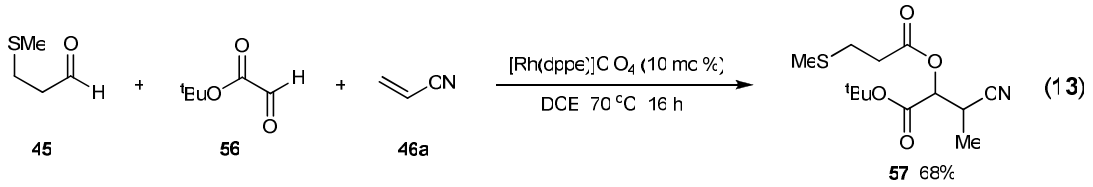


Scheme 4: Two Proposed Mechanisms for the Catalytic Reductive Aldol Reaction Employing Aldehydes as the Stoichiometric Reductants

Both mechanisms commence with the oxidative addition of Rh(I) into the aldehyde **45** C-H bond to generate chelated acyl rhodium hydride species **51.** Path A continues with the addition of **51** across acrylonitrile to generate ketone **52** which is then subjected to a Tischenko-like reduction by a second equivalent of **51** to afford the ester **53**. Alternatively, path B involves the conjugate addition of the hydride from **51** to acrylonitrile, which generates rhodium enolate **54**. Addition of the enolate to a second equivalent the starting aldehyde **45** affords the aldolate **55** which then reductively eliminates Rh(I) to provide the esterified aldol adduct **53**.

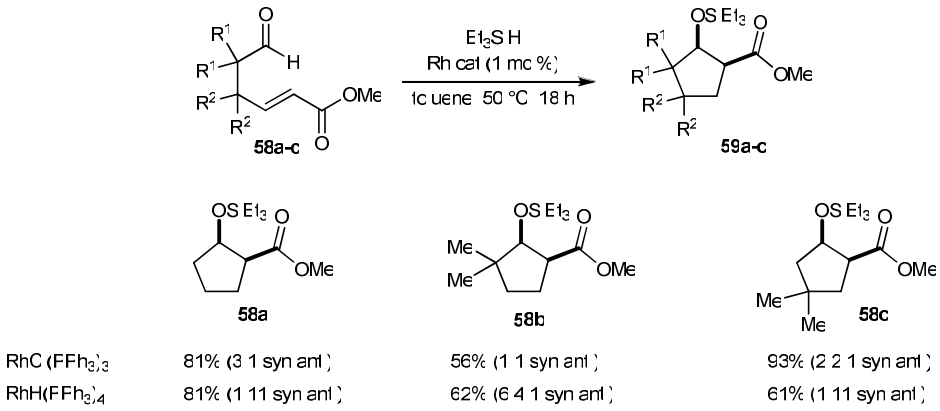
In an attempt to provide evidence for either mechanism, ketone **52** was independently prepared and then exposed to the standard reaction conditions which resulted in none of the desired aldol adduct being isolated. The possibility of an

enolate intermediate was explored by attempting to trap the enolate with an alternative aldehyde (Eq 13).



A three component reaction involving sulphide-substituted aldehyde **45**, acrylonitrile (**46a**), and t-butyl glyoxylate **56** provided acylated aldol adduct **57** in good yield. This evidence is consistent with path B.

An example of a Rh-catalysed *intra*molecular reductive aldol reaction was reported by Motherwell and co-workers.[17] Aldehydes tethered to enones *via* all-carbon linkages were cyclised to produce a selection of five- and six-membered carbocycles. Reactions were performed at 50 °C in toluene using two different rhodium salts, $RhCl(PPh_3)_3$ and $RhH(PPh_3)_4$, and Et_3SiH as the hydride source (Scheme 5).

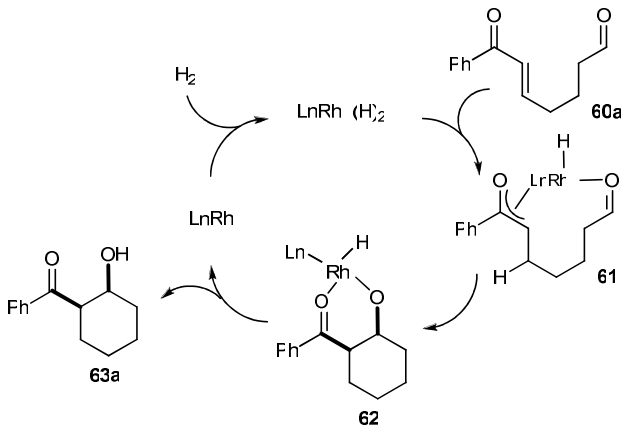


Scheme 5: Rhodium-Catalysed Intramolecular Reductive Aldol Reactions with Aldehydes Tethered to Enones

Remarkably, the use of Wilkinson's catalyst ($RhCl(PPh_3)_3$) provided the cyclised silylated cyclopentanol products **59a-c** with *syn* selectivity whereas the use of ($RhH(PPh_3)_4$) provided the desired products **59a** and **59c** in generally higher yield and with *anti* selectivity (**59b** was still *syn* selective).

1.1.2 Hydrogen-Mediated Reactions

In 2002 Krische and co-workers developed the first catalytic protocol for the reductive generation of transition metal enolates using elemental hydrogen as the terminal reductant.[18] This new chemistry was employed in the rhodium-catalysed intramolecular reductive aldol reaction of enone-tethered aldehydes. The idea was based on the assumption that the mechanism of rhodium-catalysed hydrogenation of alkenes would follow three fundamental steps (Scheme 6).



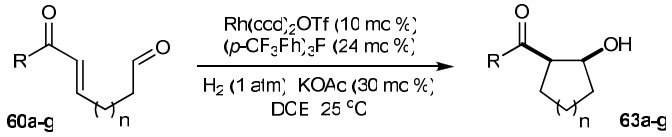
Scheme 6: Proposed Catalytic Cycle for Electrophilic Trapping

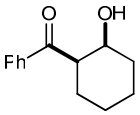
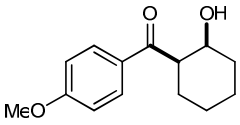
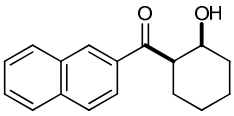
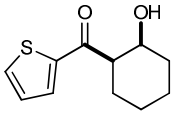
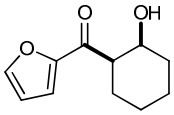
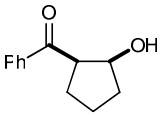
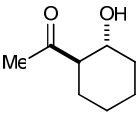
The first step involves oxidative addition of LnRh(I) to elemental hydrogen This is then followed by alkene hydrometallation to enone tethered aldehyde **60a** affording LnRh(III)(alkyl)(hydrido) intermediates **61** and **62**. Finally, an alkyl hydrogen reductive elimination affords the saturated product **63a** and LnRh(I) to close the catalytic cycle.[19] This mechanism is based on the assumption that the Rh-alkyl complex **61** will react with an electrophile.

In order to test this hypothesis, an initial screen was conducted using solutions of enone tethered aldehyde **60a** in DCE which was then exposed to various rhodium sources under 1 atm of hydrogen. Although some of the catalysts screened did produce the desired product, the undesired 1,4-conjugate reduction product was also obtained. Further screening established a protocol using KOAc as a base together with the electron-poor phosphine ligand (p-$CF_3Ph)_3P$ and $Rh(cod)_2OTf$. Using this

protocol meant the hydrogenated product of 1,4-conjugate reduction was diminished to less than 0.1% of the total yield. The scope of the reaction was examined with various enone-aldehydes (Table 7).

Table 7: Rh-Catalysed Hydrogenative Aldol Cycloreduction of Monoenone Monoaldehydes

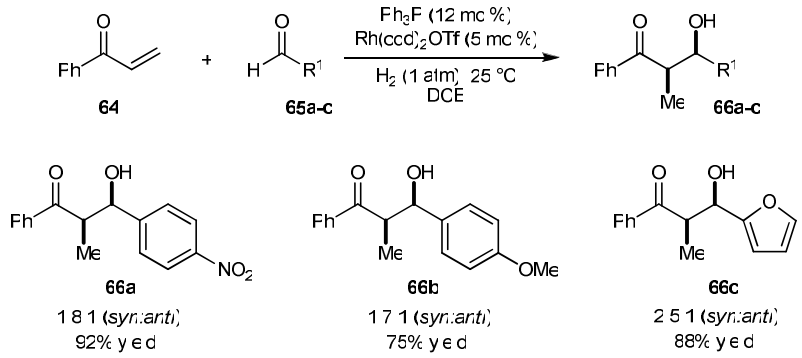


Entry	n	R	Product		Yield (%)	d.r. (syn:anti)
1	2	Ph		**63a**	89	10:1
2	2	p-MeOPh		**63b**	74	5:1
3	2	2-napththyl		**63c**	90	10:1
4	2	2-thiophenyl		**63d**	76	19:1
5	2	2-furyl		**63e**	70	6:1
6	1	Ph		**63f**	71	24:1
7	2	CH_3		**63g**	65	1:5

The intramolecular reaction proceeded well with a range of aromatic (entries 1-3), heteroaromatic (entries 4-5), and aliphatic (entry 7) enone substrates to form five- (entry 6) and six-membered rings. Interestingly, reaction with an aliphatic enone

exhibited *anti* selectivity compared to the *syn* selectivity observed in all the aromatic substrates.

Krische next expanded the scope of this methodology to include the intermolecular version of the reaction. In an initial reaction between phenyl vinyl ketone and *p*-nitrobenzaldehyde, using virtually identical conditions to those used in the intramolecular reaction, the desired product was isolated in 53% yield. Further optimisation, including the use of an excess of phenyl vinyl ketone (**64**, 1.5 equiv.), the use of the base KOAc, and the use of Ph_3P as the ligand all helped improve the yield to 92% (Scheme 7).



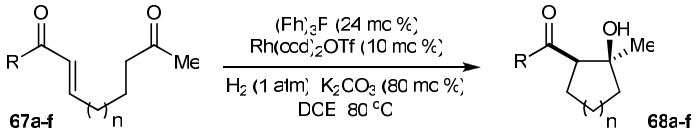
Scheme 7: Rhodium-Catalysed Intermolecular Reductive Aldol Reaction Between Phenyl Vinyl Ketone and Aldehydes

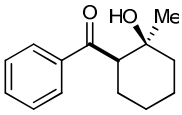
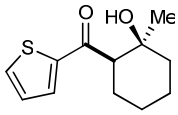
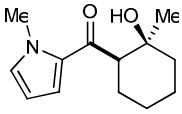
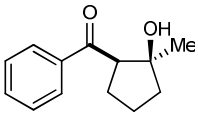
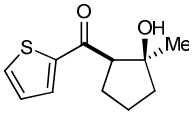
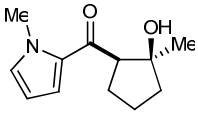
These new conditions were then applied to a range of aromatic and aliphatic aldehydes to give the reductive aldol adducts in good yields but with relatively low levels of diastereoselection up to 2.5:1 (*syn:anti*).

Having developed both *intra* and *inter*molecular versions of a new hydrogen mediated reductive aldol reaction with enone-aldehydes, Krische now sought to develop a similar system with enone-ketones.[20] This presented a greater challenge due to the lower reactivity of ketones compared to aldehydes and hence a greater problem with respect to competitive conjugate 1,4-reduction. A catalytic system similar to that used for the earlier enone-aldehyde work was employed. After optimisation experiments had been completed, the ligand was changed from (*p*-

$CF_3Ph)_3P$ to Ph_3P and K_2CO_3 was employed as the base. Reactions were conducted using aromatic and heteroaromatic enone substrates to form five- and six-membered rings (Table 8).

Table 8: Rh-Catalysed Hydrogenative Aldol Cycloreduction of Enone Tethered Ketones

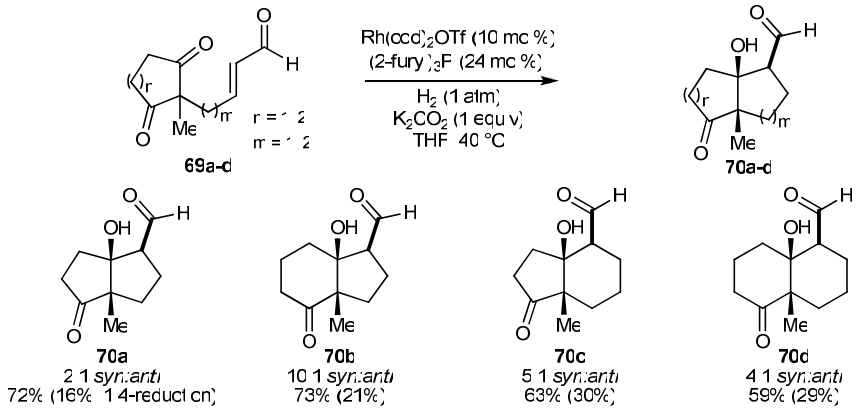


Entry	n	R	Product		Yield % Product (side product)[a]	d.r. (*syn:anti*)
1	2	Ph		**68a**	72 (20)	>95:5
2	2	2-thiophenyl		**68b**	78 (8)	>95:5
3	2	*N*-methyl pyrrolidine		**68c**	82 (12)	>95:5
4	1	Ph		**68d**	75 (8)	>95:5
5	1	2-thiophenyl		**68e**	66 (24)	>95:5
6	1	*N*-methyl pyrrolidine		**68f**	75 (11)	>95:5

a) Side product formed as the result of 1,4-conjugate reduction of starting material

These reaction conditions proved to be generally applicable, forming five- and six-membered ring products in a *syn* selective fashion. Although yields were as high as 82%, the cycloreduction product was always accompanied by minor amounts of the corresponding conjugate reduction product.

As a further extension of Krische's hydrogenation methodology, the catalytic hydrogenation-aldolisation of enals was explored.[21] The reaction conditions were optimised with changes that included the use of KOAc in place of K_2CO_3 as an additive, as well as the use of more electron deficient phosphine ligands. With these conditions in hand, the scope of the catalytic aldol cycloreduction of keto-enals was explored (Scheme 8).

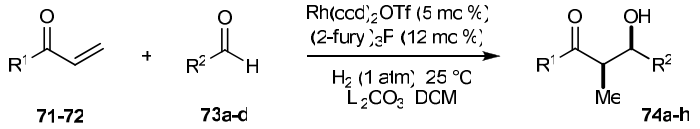


Scheme 8: Catalytic Aldol Cycloreduction of Keto-Enals

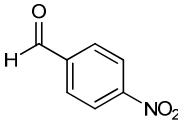
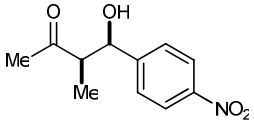
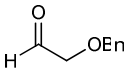
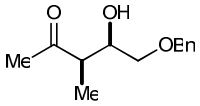
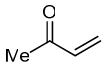
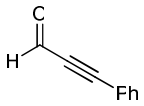
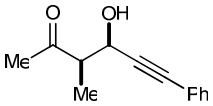
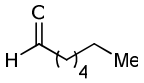
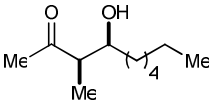
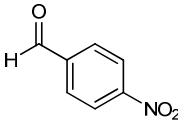
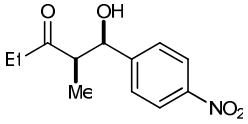
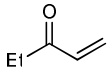
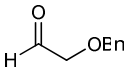
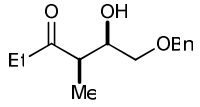
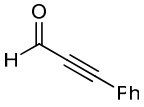
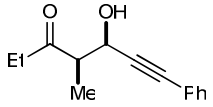
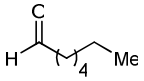
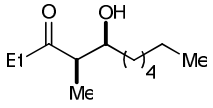
The reaction proceeds with moderate levels of diastereoselectivity to provide five-membered bicyclic aldol ring products **70a** and **70b** in 72% and 73% yield respectively. The corresponding six-membered ring products **70c** and **70d** were recovered in slightly lower yields (63% and 59% respectively). This was due to a small amount of over reduction of the starting material resulting in only the hydrogenation of the alkene.

Krische and co-workers then published further work on the coupling of enones with aldehydes using improved conditions based around the use of $(2\text{-furyl})_3P$ as the ligand.[22] Previous work was limited to the coupling of phenyl vinyl ketones and diastereoselectivity was low (Scheme 7). However, Krische found that by replacing Ph_3P with $(2\text{-furyl})_3P$, the diastereoselectivity was dramatically improved to 19:1 (*syn:anti*). These conditions were applied to a range of aldehydes using methyl vinyl ketone (**71**) and ethyl vinyl ketone (**72**) as pro-nucleophiles (Table 9).

Table 9: Diastereoselective Reductive Aldol Couplings Between Vinyl Ketones and Aldehydes



71-72 73a-d 74a-h

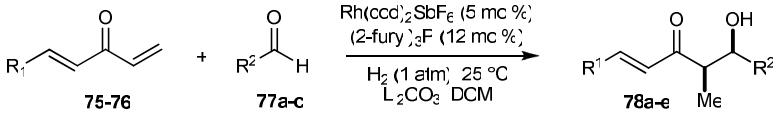
Entry	Enone	Aldehyde	Product	Yield (%)	d.r. (*syn:anti*)
1		 **73a**	 **74a**	91	16:1
2		 **73b**	 **74b**	90	17:1
3	 **71**	 **73c**	 **74c**	65	8:1
4		 **73d**	 **74d**	62	10:1
5		 **73a**	 **74e**	90	28:1
6	 **72**	 **73b**	 **74f**	88	18:1
7		 **73c**	 **74g**	70	10:1
8		 **73d**	 **74h**	60	19:1

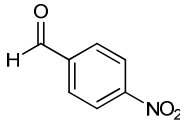
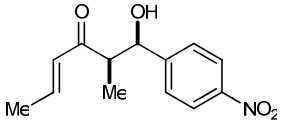
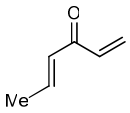
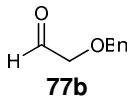
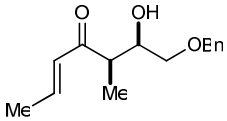
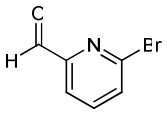
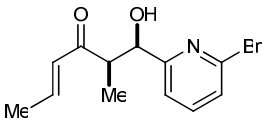
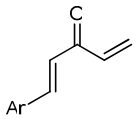
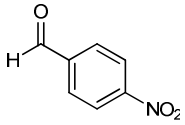
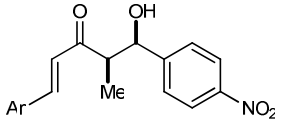
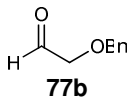
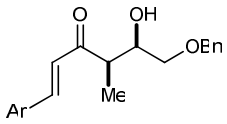
The reaction is tolerant of a wide range of aromatic, benzylic, α,β-unsaturated, and aliphatic aldehydes. Reactions performed with ethyl vinyl ketones (entries 5-8) exhibited generally improved diastereoselectivity presumably due to an enhanced kinetic and thermodynamic preference for the formation of the *Z*-enolate due to increased $A_{1,2}$-strain. The high chemoselectivity of the reaction is demonstrated by

the formation of **74c** and **74g** where the alkyne functionality remains untouched by the reductive conditions.

Krische and co-workers further extended their study to encompass the intermolecular reductive aldol reaction of vinyl ketones with aldehydes by exploring the comparative reactivity of divinyl ketones.[23] Both crotyl vinyl ketone **75** and *p*-(dimethylamino)styryl vinyl ketones **76** were reacted with different aldehydes. It was found that reaction occurred at the less substituted vinyl moiety to deliver predominately *syn*-aldol products with good yields and high diastereoselectivities (Table 10).

Table 10: Diastereoselective Reductive Aldol Couplings Between Divinyl Ketones and Aldehydes



Entry	Enone	Aldehyde	Product	Yield (%)	d.r. (syn:anti)
1		 **77a**	 **78a**	82	13:1
2	 **75**	 **77b**	 **78b**	80	9:1
3		 **77c**	 **78c**	94	11:1
4	 **76**	 **77a**	 **78d**	93	10:1
5		 **77b**	 **78e**	90	10:1

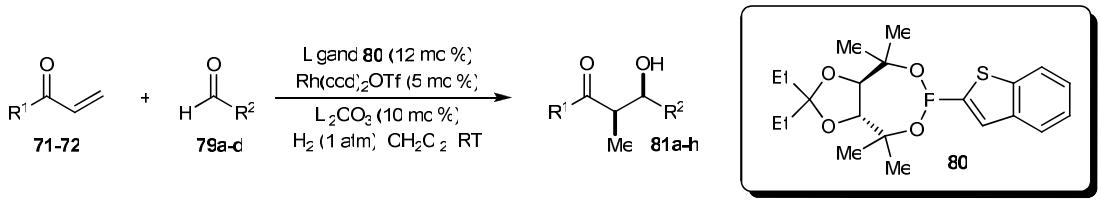
Ar = *p*-dimethylaminophenyl

Results obtained were similar to those obtained with methyl (**71**) and ethyl vinyl ketones (**72**) (see Table 9). Both high yields and high diastereoselectivities were observed for a range of aldehydes. In addition, over-reduction was not observed unless the reaction was allowed to continue after the consumption of the aldehyde.

In 2008, Krische and co-workers reported a rhodium-catalysed enantioselective reductive aldol reaction using vinyl ketones as pronucleophiles.[24] Until now, all enantioselective examples of reductive aldol reactions had employed esters as the pronucleophile. Using a TADDOL-like phosphonite ligand, the structure of which had been obtained through screening, Krische was able to effect reaction between

both methyl (**71**) and ethyl vinyl ketones (**72**) with a range of aldehyde electrophiles (Table 11).

Table 11: Diastero- and Enantioselective Reductive Aldol couplings of Vinyl Ketones to Aldehydes

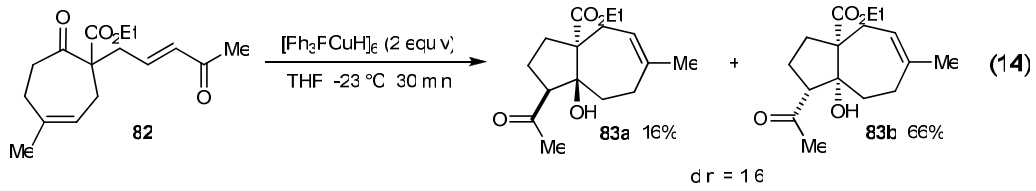


Entry	Vinyl Ketone	Aldehyde	Product	Yield (%)	ee (%)	d.r. (*syn:anti*)
1		**79a**	**81a**	70	90	25:1
2		**79b**	**81b**	79	87	11:1
3	**71**	**79c**	**81c**	85	86	15:1
4		**79d**	**81d**	85	91	25:1
5		**79a**	**81e**	76	90	22:1
6		**79b**	**81f**	83	88	25:1
7	**72**	**79c**	**81g**	97	90	25:1
8		**79d**	**81h**	96	88	22:1

The reaction tolerates a wide range of aldehydes including α-(hetero)aryl aldehydes (entries 1-3 and 5-7) and α-heteroatom substituted aldehydes (entries 4 and 8). Products were obtained in good to excellent yield, dr, and ee whether methyl (**71**) or ethyl vinyl ketones (**72**) were used as the pro-nucleophile.

1.2 Copper-Catalysed and Mediated Reductive Aldol Reactions

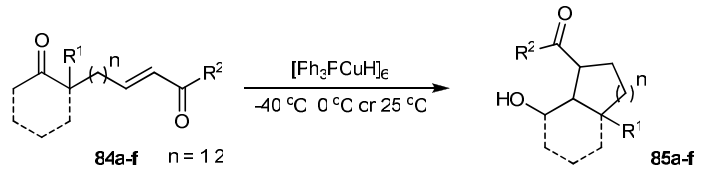
Conjugate reduction of α,β-unsaturated carbonyl compounds with a copper species was first reported in 1988 by Stryker and co-workers.[25] Stryker's reagent ($[(Ph_3P)CuH]_6$), can reduce α,β-unsaturated carbonyl compounds while remaining inert to simple olefins. However, it was not until 1998 that Strykers reagent was employed in a reductive aldol reaction when Chiu and co-workers found it could be used for the key step in the synthesis of pseudolaric acid A (Eq 14).[26]



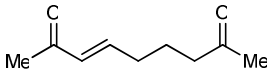
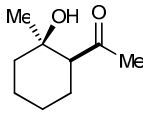
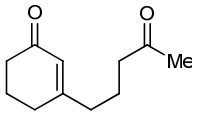
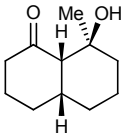
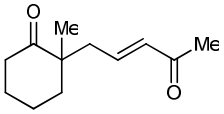
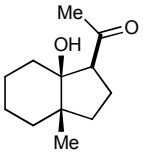
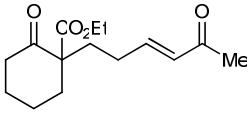
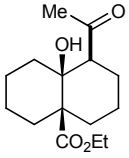
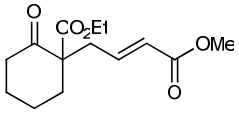
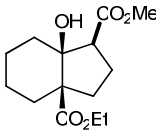
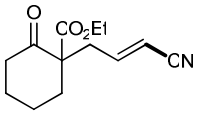
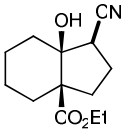
Chiu found that the use of a stoichiometric quantity of Strykers reagent at room temperature promoted the reductive aldol cyclisation of **82**, to form a mixture of *trans*- and *cis*-fused ring systems (**83a** and **83b** respectively). Performing the reaction at -23 ^{o}C improved the diastereoselectivity to the extent that 66% of the major *cis* isomer **83b** could be isolated.

Chiu then extended the scope of this methodology, demonstrating its use in the synthesis of five- and six-membered carbocycles. The reaction can also be carried out in one pot, with high levels of diastereoselectivity (Table 12).[27]

Table 12: Intramolecular Reductive Aldol Reactions Using Stoichiometric Amount of Stryker's Reagent



84a-f n = 1 2 85a-f

Entry	Substrate	Temp (°C)	Product[a]	Yield (%)[a]
1	 **84a**	- 40	 **85a**	80
2	 **84b**	0	 **85b**	19[b]
3	 **84c**	- 40	 **85c**	66
4	 **84d**	- 40	 **85d**	93
5	 **84e**	25	 **85e**	84
6	 **84f**	25	 **85f**	66

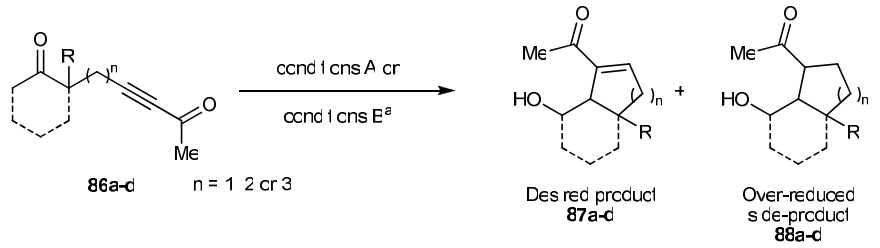
a) Only one diastereomer observed b) 69% recovered substrate also obtained.

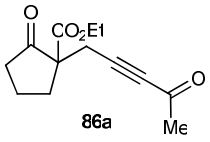
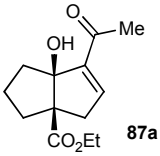
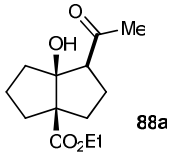
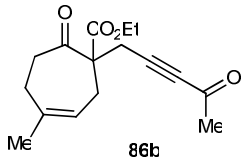
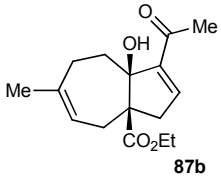
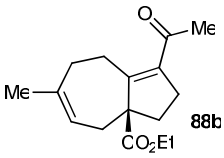
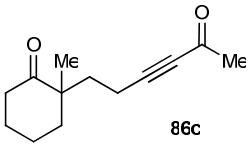
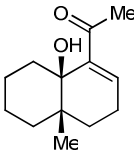
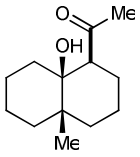
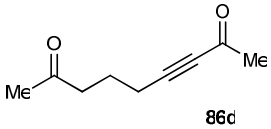
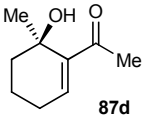
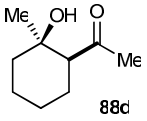
A variety of substrates underwent conjugate reduction and cyclisation to provide β-hydroxyketones in good to excellent yields (**85a**-**85f**). Reaction temperatures of -40 ^{o}C were necessary to reduce the problem of dehydration at the two new stereocentres and thus ensure high yields. The presence of a larger substituent than a CH_2 unit α to the double bond affects reactivity significantly (entry 2) as does conjugation of the

double bond to an ester or nitrile. In these cases, elevated temperatures are required to ensure full conversion (entries 2, 5 and 6).

Chiu and co-workers then moved on to develop the first catalytic reductive aldol reaction catalysed by a copper complex.[28] It had already been reported that copper hydride from Stryker's reagent could be regenerated using silanes.[29] Using 10 mol% of Stryker's reagent, together with a stoichiometric amount of the hydride source PMHS (polymeric hydrosiloxane), Chiu found this combination would induce the aldol cyclisation of alkynediones (Table 13).

Table 13: Intramolecular Reductive Aldol Reactions Using catalytic and stoichiometric Amounts of Stryker's Reagent



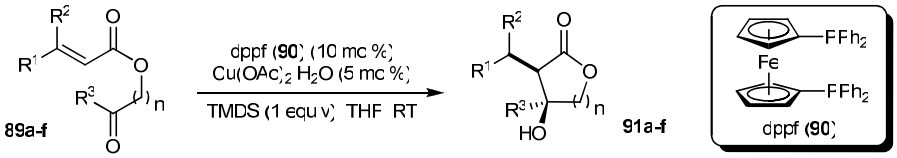
Entry	Substrate	A/B	Product[b]	Side-Product	Yield (%)	
1A		A			54[c]	(13)[d]
1B	86a	B	87a	88a	58	(39)
2A		A			48	(16)
2B	86b	B	87b	88b	65	(6)
3A		A			53	(16)
3B	86c	B	87c	88c	56	(25)
4A		A			62	(14)
4B	86d	B	87d	88d	46	(0)

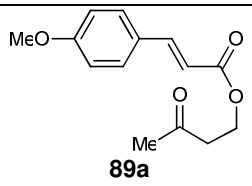
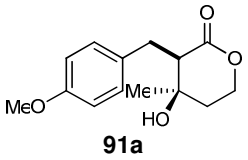
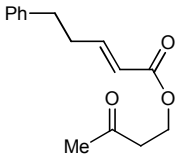
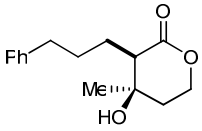
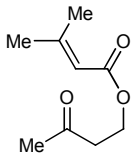
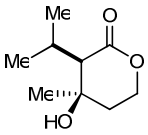
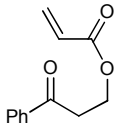
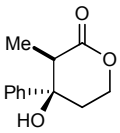
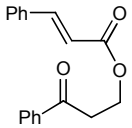
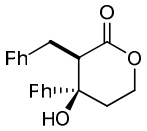
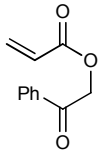
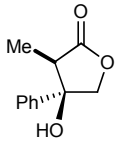
a) Conditions A: $[(Ph_3P)CuH]_6$ (1.5 equiv), toluene. Conditions B: $[(Ph_3P)CuH]_6$ (10 mol%), PMHS (2 equiv), toluene. b) Only one diastereomer observed c) Yield of product d) Yield of over-reduced side product

The reaction proceeds to form bicyclic products with comparable yields and reaction times regardless of whether $[(Ph_3P)CuH]_6$ is used in a stoichiometric or catalytic fashion. A significant problem is over-reduction of the product where either the remaining conjugated double bond is reduced (entries 1,3 and 4) or dehydration causes migration of the double bond, destroying one of the stereocentres (entry 2).

In 2005, our research group reported the first enantioselective example of the formation of ring systems *via* a reductive aldol methodology.[30] Moisture- and air-stable $Cu(OAc)_2 \cdot H_2O$ was used along with the ligand dppf (**90**) and 1,1,3,3-tetramethylsiloxane (TMDS) as a stoichiometric hydride source. α,β-Unsaturated esters tethered to a ketone moiety underwent cyclisation to form both five- and six-membered β-hydroxylactones in moderate to good yields and with very high *syn*-selectivities (>95:5) (Table 14).

Table 14: Intramolecular Reductive Aldol Reactions Using $Cu(OAc)_2 \cdot H_2O$ with DPPF and TMDS[a]



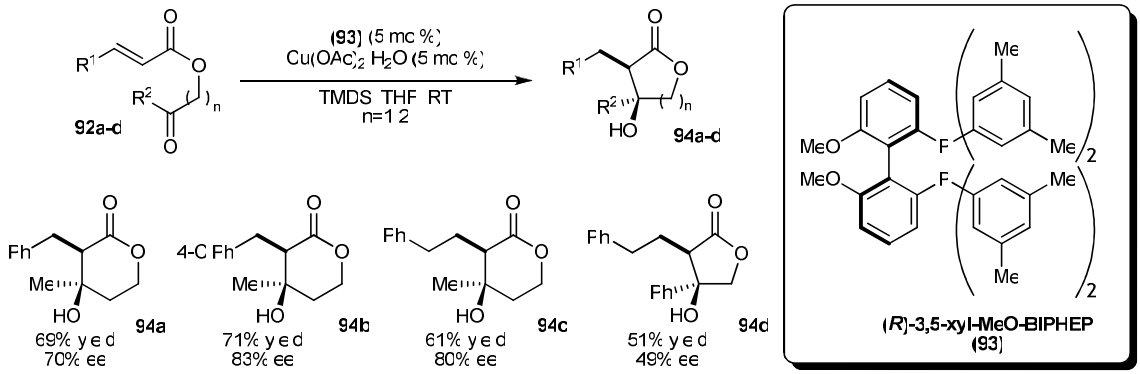
Entry	Substrate	Product[a]	Yield (%)
1	 **89a**	 **91a**	61
2	 **89b**	 **91b**	61
3	 **89c**	 **91c**	62
4	 **89d**	 **91d**	71
5	 **89e**	 **91e**	47[b]
6	 **89f**	 **91f**	69

a) Only 1 diastereomer of product observed by ^{1}H NMR analysis. b) Product formed as an 8:1 mixture of inseparable diastereomers.

A range of β-hydroxy-δ-valerolactones were synthesised from α,β-unsaturated ester components containing aromatic (entries 1-2) and alkyl (entry 3) substituents. Replacement of the methyl ketone with a phenyl ketone also permitted cyclisation to take place (entries 4 and 5). In addition, five-membered rings could be formed (entry

6) despite these cyclisations being formally disfavoured 5-(enolendo)-*exo-trig* ring closures according to Baldwins rules.[31]

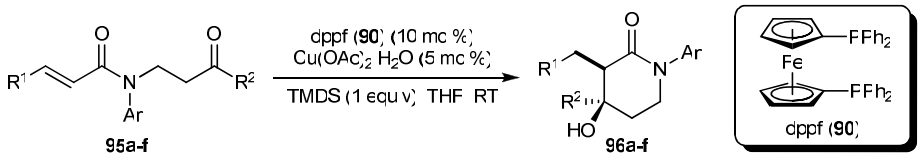
The reaction was rendered asymmetric by replacing dppf (**90**) with the chiral bisphosphine ligand **93** resulting in enantioselectivities of up to 83% (Scheme 9).

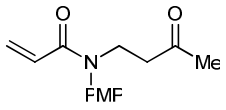
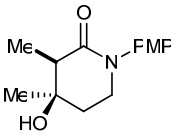
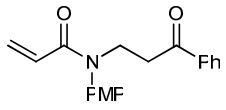
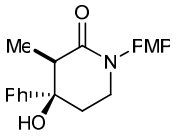
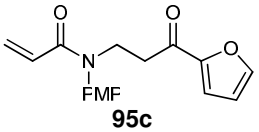
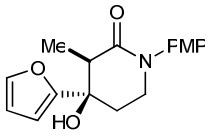
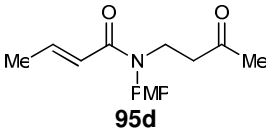
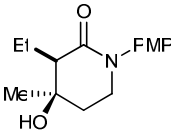
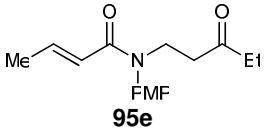
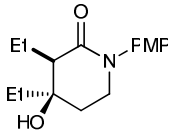
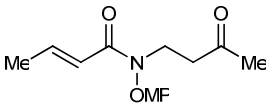
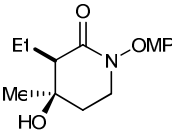


Scheme 9: Copper-Catalysed Asymmetric Intramolecular Reductive Aldol Reactions

This methodology was extended through the use of the corresponding amide linkage in place of an ester to form six-membered lactams.[32] Under identical reaction conditions to those applied above, a range of α,β-unsaturated amides tethered to a ketone moiety underwent smooth cyclisation (Table 15).

Table 15: Reductive Aldol Cyclisations to Form 4-Hydroxypiperidin-2-ones[a]



Entry	Substrate	Product[a]	Yield (%)
1	 **95a**	 **96a**	66
2	 **95b**	 **96b**	69
3	 **95c**	 **96c**	53
4	 **95d**	 **96d**	55
5	 **95e**	 **96e**	52
6	 **95f**	 **96f**	70

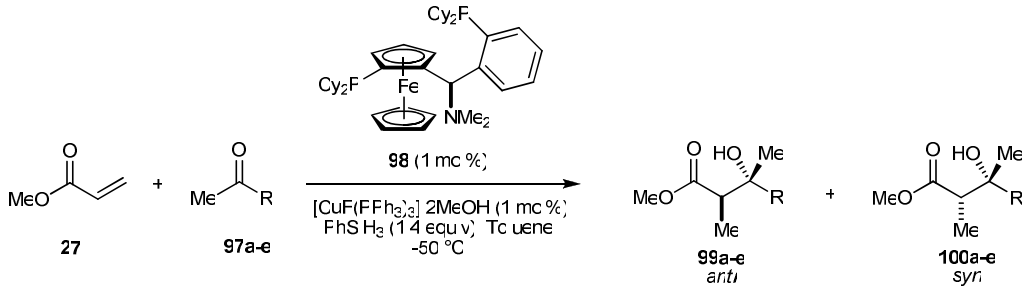
a) Only one diastereomer of product observed by ^{1}H NMR spectroscopy.

The reaction tolerated substitution at the ketone component well, with alkyl (Entries 1 and 4-6), aromatic (Entry 2) and heteroaromatic (Entry 3) ketones reacting readily. The reaction was less tolerant of substitution of the α,β-unsaturated carbonyl component with acryloyl amides generally exhibiting the highest reactivity (entries 1-3). Although crotonoyl amides also underwent cyclisation (Entries 4–6), reaction rates and conversions were generally lower. A limitation of this methodology is that

as the size of the substituent at the β-position is increased further, both conjugate and ketone reduction becomes a problem.

In 2006, Riant and co-workers reported the first asymmetric copper-catalysed intermolecular reductive aldol reaction between methyl acrylate and ketones.[33] Using a substoichiometric amount of [$CuF(PPh_3)_3$·2MeOH] together with the Cy-Taniaphos-ligand **98** and $PhSiH_3$ as a stoichiometric hydride source, it was possible to achieve the desired aldol products with both high yield and selectivities (Table 16).

Table 16: Copper-Catalysed Asymmetric Intermolecular Reductive Aldol Reactions Between Acrylate and Ketones

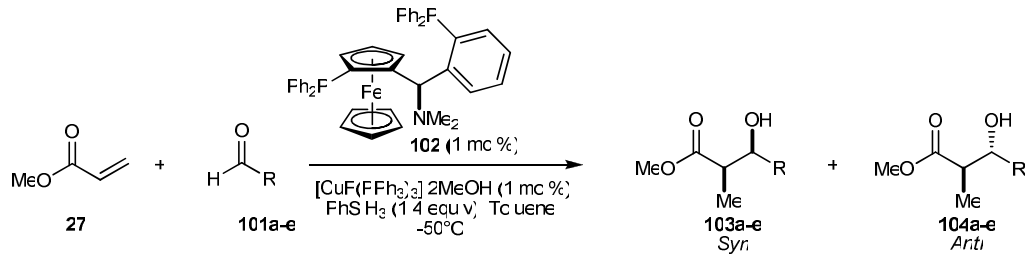


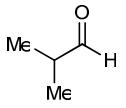
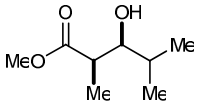
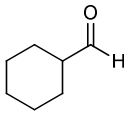
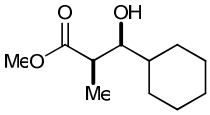
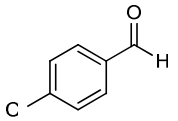
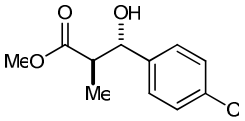
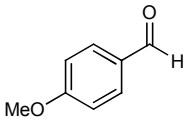
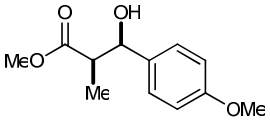
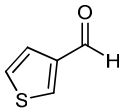
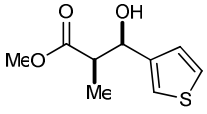
Entry	Ketone	Product (*anti*)	d.r.[a]	Yield (%)[b]	ee (%)[c]
1	**97a**	**99a**	92:8	98	95
2	**97b**	**99b**	91:9	88	92
3	**97c**	**99c**	92:8	31	90
4	**97d**	**99d**	88:12	70	82
5	**97e**	**99e**	96:4	94	90

a) *Anti* as major isomer b) yield of *anti* isomer c) ee of *anti* isomer

The reaction achieves very high levels of stereoselection in generally high yields and only requires very low catalyst loading (1 mol% of copper and ligand). The limitation of this methodology is that it only works with methyl acrylate (**27**) as a pro-nucleophile and aromatic (Entries 1-4) or heteroaromatic methyl ketones (Entry 5) as electrophiles. Riant and co-workers extended this methodology to encompass aldehydes as the electrophile.[34] The conditions that had worked so well with ketones (Table 16) were used again but after some optimisation work, the ligand was changed to the Ph-Taniaphos-ligand **102** (Table 17).

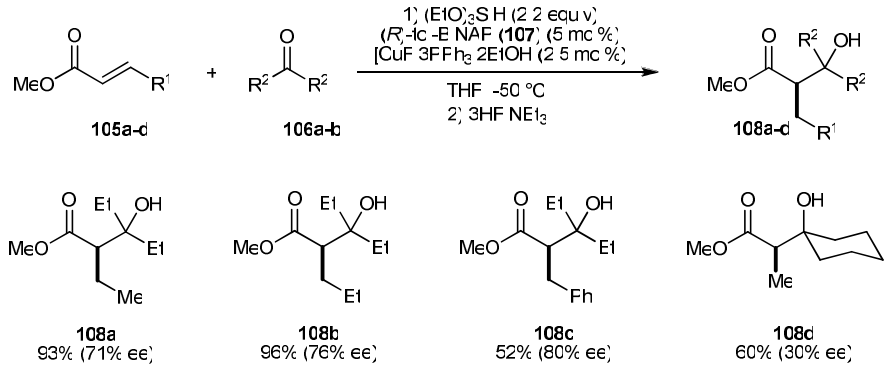
Table 17: Copper-Catalysed Asymmetric Intermolecular Reductive Aldol Reactions Between Acrylate and Aldehydes



Entry	Aldehyde	Major Diastereomer of Product	d.r. (*syn:anti*)	ee (*syn*)	ee (*anti*)
1	 **101a**	 **103a**	64:36	73	26
2	 **101b**	 **103b**	57:43	86	70
3	 **101c**	 **103c**	44:56	85	69
4	 **101d**	 **103d**	60:40	68	72
5	 **101e**	 **103e**	51:49	86	76

The reaction tolerates aliphatic (Entries 1-2), aromatic (Entries 3-4) and heteroaromatic (Entry 5) aldehydes furnishing the desired aldol products in good to excellent enantioselectivities with almost complete conversion. However, a major drawback with this reaction methodology is that it suffers from very poor diastereoselectivity.

At about the same time, and independently from Riant, Shibasaki and co-workers also reported a copper-catalysed intermolecular reductive aldol reaction between esters and ketones.[35] The conditions used were similar to those used by Riant except that (*R*)-tol-BINAP (**107**) was used instead of the Taniaphos ligands **98** or **102** and $(EtO)_3SiH$ was used in the place of Ph_3SiH. During optimisation studies, only relatively poor levels of enantio- and diastereoselectivity were achieved from prochiral ketones. For this reason, the scope of the reaction with regard to asymmetric induction at the α-position was examined using symmetrical ketones (Scheme 10).



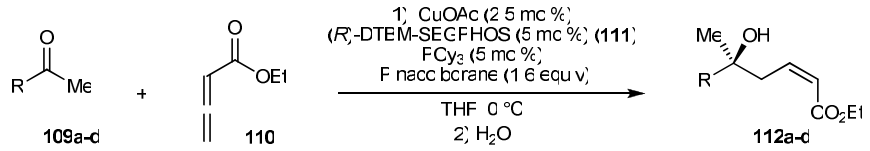
Scheme 10: Asymmetric Induction at α-position in Reductive Aldol Reactions with Symmetric Ketones

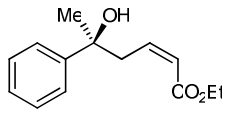
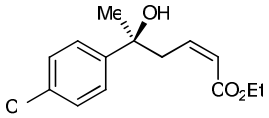
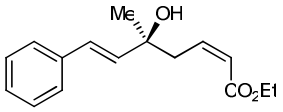
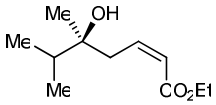
Moderate to high levels of asymmetric induction at the α-position were realised in reactions where the β-carbon was substituted with methyl, ethyl or phenyl groups (**108a**-**108c**). However, when other symmetric ketones were reacted, only low levels of enantioselectivity were observed (**108d**, 30% ee).

Shibasaki and co-workers extended this methodology by developing the intermolecular reductive aldol reaction between allenic esters and ketones.[36] This posed a particular challenge with regard to selectivity because allenic ester pro-

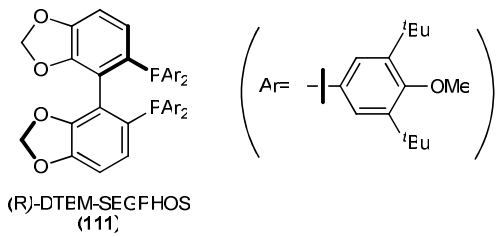
nucleophiles can attack from either γ- or α-positions. However, Shibasaki found, that by simply changing the metal-ligand combination, access could be gained to both γ- and α-linked aldol adducts. By using CuOAc, in combination with (*R*)-DTBM-SEGPHOS (**111**), pinacolborane as a reductant and PCy_3 as an additive, very high levels of the γ-cis-selective products were obtained with a selection of ketones (Table 18).

Table 18: γ-cis-Selective Reductive Aldol Reactions to Ketones



Entry	R	Product	γ:α-ratio[a]	Yield[a] (%)	ee (%)
1	Phenyl	 **112a**	25:1	96	99
2	*p*-Cl-Phenyl	 **112b**	13:1	93	98
3	Cinnamyl	 **112c**	30:1	97	84
4	isopropyl	 **112d**	>8:1	80	98

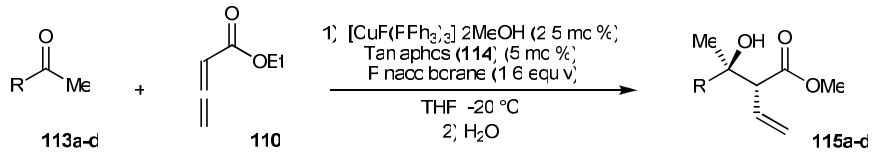
a) Determined by ^{1}H NMR spectroscopy



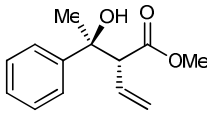
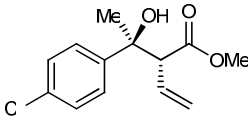
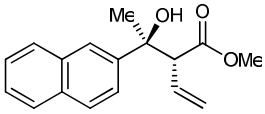
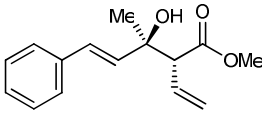
(*R*)-DTBM-SEGPHOS (**111**)

By changing the catalyst to $CuF{\cdot}3PPh_3$ in combination with TaniPhos-type ligand **114**, the α-selective aldol products can be generated in high yields, with good diastereoselectivity and with high levels of enantioselectivity for a large variety of ketones (Table 19).

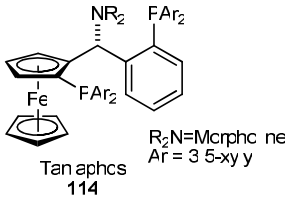
Table 19: α-Selective Reductive Aldol Reaction to Ketones



113a-d 110 115a-d

Entry	R	Product	dr (*Syn:anti*)[a]	Yield[a] (%)	ee (%)
5	Ph	 **115a**	10:1	90	84
6	*p*-Cl-Phenyl	 **115b**	8:1	89	83
7	2-napthyl	 **115c**	10:1	91	84
8	cinnamyl	 **115d**	9:1	87	67

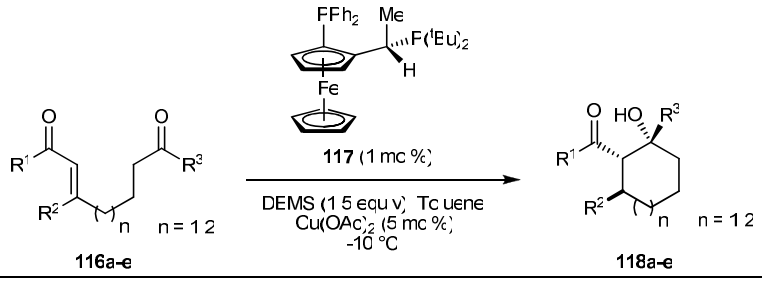
a) Determined by NMR spectroscopy

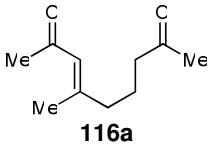
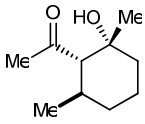
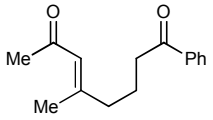
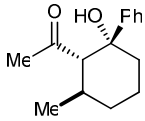
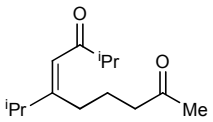
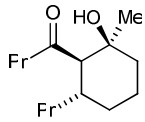
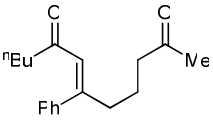
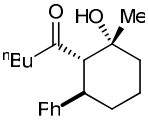
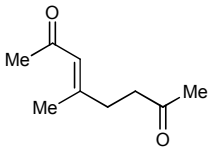
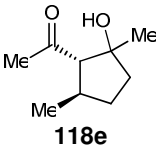


Very recently, Lipshutz and co-workers reported a copper catalysed intramolecular reductive aldol reaction that generated three contiguous stereocentres.[37] Using 5

mol% of $Cu(OAc)_2$, together with the Josiphos ligand **117** and DEMS (diethoxymethylsilane) as a stoichiometric reductant, Lipshutz was able to effect the cyclisation of β-substituted α,β-unsaturated ketones tethered to another ketone via a hydrocarbon linkage. These conditions were applied to a range of β,β-disubstituted enones (Table 20).

Table 20: Copper-Catalysed Asymmetric Cycloreductions



Entry	Enone	Product	Yield (%)	ee (%)
1	 **116a**	 **118a**	91	96
2	 **116b**	 **118b**	77	97
3	 **116c**	 **118c**	66	84
4	 **116d**	 **118d**	83	77
5	 **116e**	 **118e**	75[a]	97,92

a) Combined isolated yield for diastereomers (dr = 59:41).

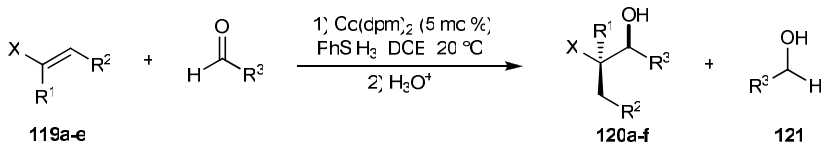
Reactions proceeded in generally high yield and high enantiomeric excess. Both *E*-(entries 1-2, 4-5) and *Z*-enones (entry 3) were employed successfully. In addition, the

reaction tolerates substitution at the β-carbon of both aliphatic (entry 4) and aromatic groups (entry 4). The cyclisation of five-membered rings was also possible although this gave rise to two isolable diastereomers.

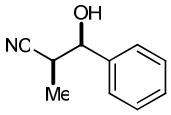
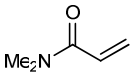
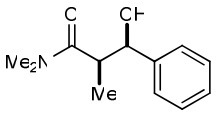
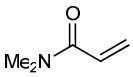
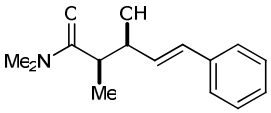
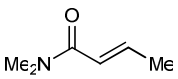
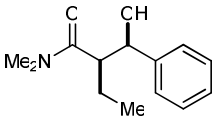
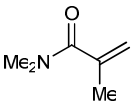
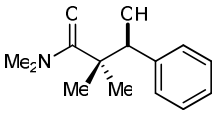
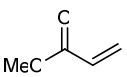
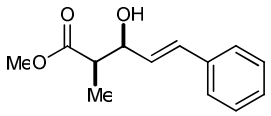
1.3 Cobalt-Catalysed Reductive Aldol Reactions

Soon after Revis and Hilty reported the first reductive aldol reaction, Mukaiyama and co-workers reported the first cobalt-catalysed reductive aldol reaction.[38] Using substoichiometric amounts of $Co(dpm)_2$ as catalyst and stoichiometric amounts of phenylsilane as reductant, they were able to effect reaction between α,β-unsaturated nitriles, amides and esters with aldehydes (Table 21).

Table 21: Cobalt-Catalysed Intermolecular Reductive Aldol Reactions.



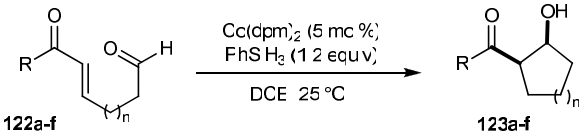
119a-e 120a-f 121

Entry	Nucleophile	Product	Yield (%)	dr (*syn:anti*)	121 (%)
1	 **119a**	 **120a**	93	(1:1)	2
2	 **119b**	 **120b**	95	(4:1)	3
3	 **119b**	 **120c**	96	(72:28)	trace
4	 **119c**	 **120d**	72	(70:30)	10
5	 **119d**	 **120e**	50	-	31
6	 **119e**	 **120f**	80	(1:1)	10

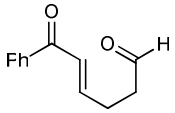
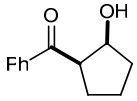
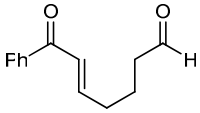
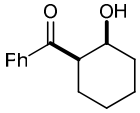
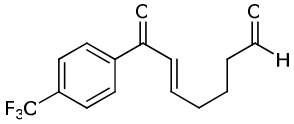
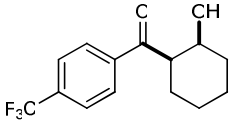
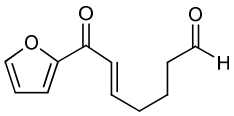
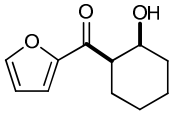
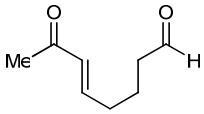
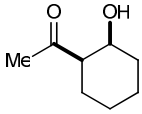
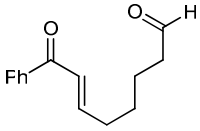
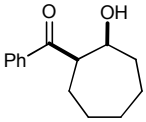
The reactions proceeded well with both substituted (entries 4 and 5) and unsubstituted pro-nucleophiles. Significantly, for the first time, reaction products were obtained with modest *syn* diastereoselectivity (entries 2-4) which demonstrated the potential of the reductive aldol reaction as a useful tool in organic synthesis.

In 2001, Krische and co-workers extended this work by describing the first example of a cycloreduction reaction.[39] Diastereoselectivities described in Mukaiyama's work were poor but Krische reasoned that in the intramolecular process, the geometrical requirements would be more stringent and so higher diastereoselectivity would be expected. When enone-aldehydes were exposed to Mukaiyama's original conditions, the desired products were isolated with exceptionally high levels of the *syn* diastereomer (>99:1) (syn:anti) (Table 22).

Table 22: Cobalt-Catalysed Intramolecular Reductive Aldol Reactions of Enone-Aldehydes



122a-f 123a-f

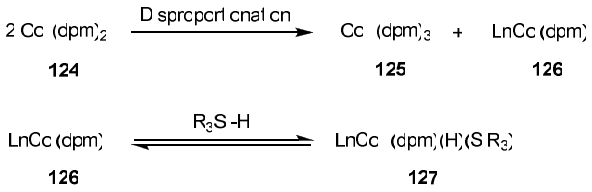
Entry	Substrate	Product	Yield (%)
1	 **122a**	 **123a**	70
2	 **122b**	 **123b**	87
3	 **122c**	 **123c**	72
4	 **122d**	 **123d**	75
5	 **122e**	 **123e**	38
6	 **122f**	 **123f**	35

Note: In all cases, only the *cis* diastereomer was observed

Aromatic enone-aldehydes cyclised smoothly to give five- and six-membered rings in good yield (entries 1-4). However, when aliphatic enone-aldehydes were used, the yield was much reduced (entry 5). It was also possible to cyclise a seven-membered ring albeit in low yield (entry 6).

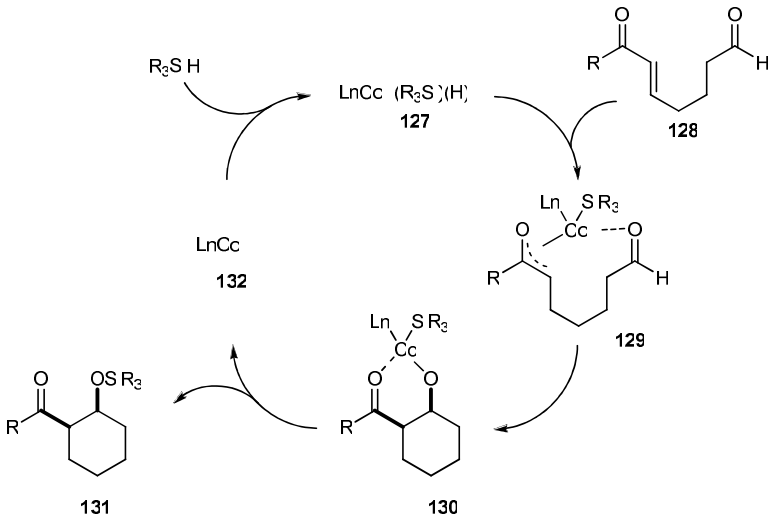
Krische and co-workers then conducted a detailed mechanistic study of the enone-aldehyde intramolecular aldol cycloreduction.[40] Initially, they attempted to determine how the hydrido-metal intermediate, required for the initiation of the catalytic cycle,

was formed from $Co(dpm)_2$ which has a formal oxidation state of II. Direct oxidative addition of silane to Co(II) was ruled out due to the instability of the resultant Co(IV) intermediate.[41] Therefore two possibilities remained: i) a single electron oxidative addition of silane, followed by reductive elimination to produce Co(I), then a two-electron oxidative addition to silane or ii) disproportionation of Co(II) followed by two-electron oxidative addition of silane to Co(I). This second possibility is illustrated in Scheme 11. Disproportionation of Co(II) was already well documented.[42] In addition, the disproportionation pathway was supported by HRMS analysis of $Co(dpm)_2$ in the presence and absence of $PhMeSiH_2$.



Scheme 11: Disproportionation Mechanism Forming a Co(III) Species.

Having established the most likely route to the formation of the hydrido-metal intermediate, Krische now postulated a mechanism for the reaction (Scheme 12).

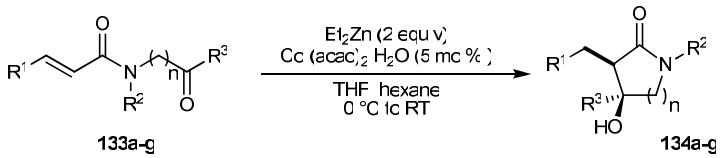


Scheme 12: Proposed Mechanism of the Enone-Aldehyde Intramolecular Reductive Aldol Reaction

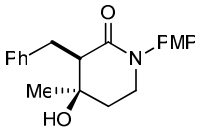
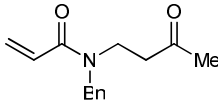
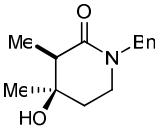
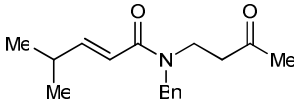
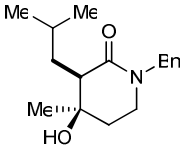
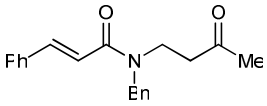
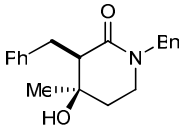
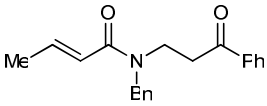
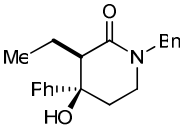
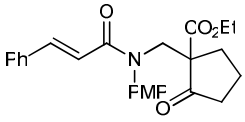
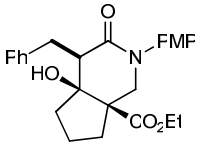
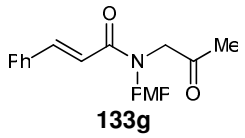
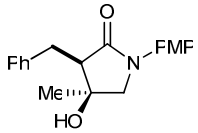
Oxidative addition of silane to LnCo(I) **132** affords hydrido-cobalt species **127**. Hydrometallation of the enone **128** provides cobalt enolate **129** which undergoes carbonyl addition to the tethered aldehyde giving cobalt-aldolate **130**. Oxygen-silicon reductive elimination liberates the aldol product as a silyl ether **131**, and regenerates the LnCo(I) catalyst **132** to complete the catalytic cycle.

In 2006, our research group reported a new methodology for the intramolecular reductive aldol cyclisations of α,β-unsaturated amides tethered to ketones.[43] Earlier work with copper catalysts had suffered from a number of limitations including moderate yields and limited substrate scope. After exhaustive screening, it was found that many of these limitations could be overcome with the use of $Co(acac)_2 \cdot 2H_2O$ as the pre-catalyst and Et_2Zn as the stoichiometric reductant. With these improved conditions in hand, the reaction scope was examined (Table 23).

Table 23: Cobalt-Catalysed Intramolecular Reductive Aldol Cyclisations of Amides Tethered to Ketones



133a-g 134a-g

Entry	Substrate	Product	dr[a]	Yield(%)[b]
1	 **133a**	 **134a**	12:1	89
2	 **133b**	 **134b**	9:1	88
3	 **133c**	 **134c**	>19:1	99
4	 **133d**	 **134d**	>19:1	97
5	 **133e**	 **134e**	>19:1	94
6[c]	 **133f**	 **134f**	>19:1	88
7	 **133g**	 **134g**	8:1	56

a) Determined by ^{1}H NMR spectroscopic analysis. b) Isolated yields of the major diastereomer c) $CoCl_2$ (5 mol%) and Cy_2PPh (5.5 mol%) used in place of $Co(acac)_2{\cdot}2H_2O$

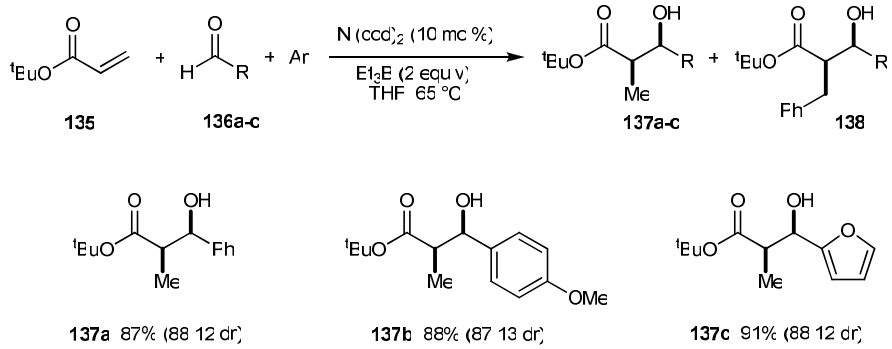
Substrates containing a wide range of substitution at both the α,β-unsaturated amide and the ketone underwent cyclisation to give β-hydroxylactam products in generally excellent yields and high diastereoselectivities (entries 1-6). The use of the standard

reaction conditions resulted in low yields and a complex mixture of unidentified products when attempts were made to cyclise substrate **133f** (entry 6). However, the use of $CoCl_2$ and the electron-rich phosphine ligand Cy_2PPh in place of $Co(acac)_2 \cdot 2H_2O$ allowed the reaction to proceed with complete conversion.

This methodology was subsequently used in the development of an *inter*molecular version of the reaction. This work is the subject of chapters 2 and 3.

1.4 Nickel-Catalysed Reductive Aldol Reactions

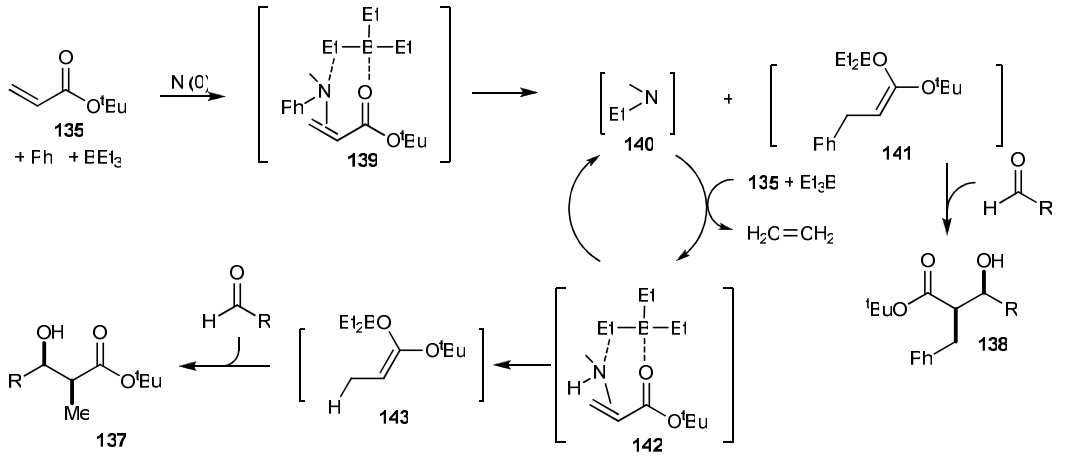
In 2007 Montgomery and co-workers disclosed the first example of a nickel-catalysed reductive aldol reaction.[44] Although the reaction itself did not improve on existing methodology, it did exhibit a remarkable dependence on an aryl iodide additive. Investigation into the reason for this dependence revealed interesting mechanistic details. $Ni(cod)_2$ and Et_3B were used to catalyse the reaction of *t*-butyl acrylate (**135**) with aldehydes with the presence of phenyl iodide as an additive (Scheme 13).



Scheme 13: Nickel-Catalysed Reductive Aldol Reactions Between α,β-Unsaturated Esters and Aldehydes

As well as the reductive aldol products **137a**, **137b**, and **137c**, a small amount of the side product **138**, formed from phenyl addition followed by aldol coupling, was observed every time the reaction was performed. When the reaction was performed without the presence of phenyl iodide, none of the expected reductive aldol product was isolated and only starting materials were cleanly recovered. Based on these

findings, Montgomery proposed a possible mechanistic sequence that could explain all these observations (Scheme 14).

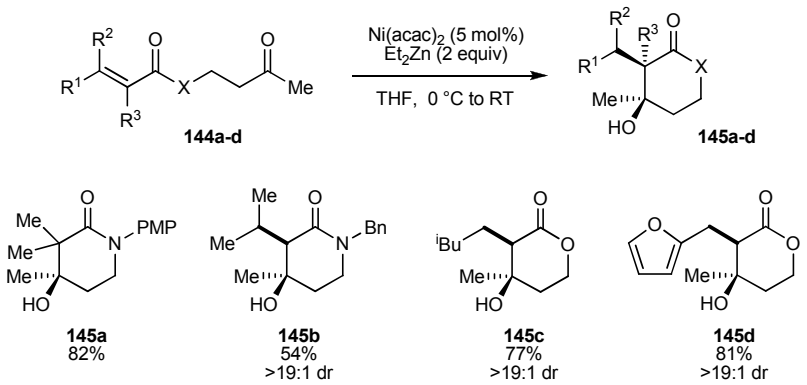


Scheme 14: Proposed Mechanism for Nickel-Catalysed Initiation and Addition Steps

Oxidative addition of Ni(0) to the aryl iodide followed by coordination of *t*-butyl acrylate (**135**) and Et_3B would afford intermediate **139**. Reorganisation of **139** provides ethyl(iodo)nickel species **140** and boron enolate **141**. The enolate **141** can now undergo *syn* aldol addition with the aldehyde to yield aldol product **138** which, it can be seen, is solely derived from this required initiation step. The ethyl(iodo)nickel species **140** is free to complex with additional acrylate **135** and Et_3B, concomitant with loss of ethylene to generate nickel hydride **142**. Reorganisation of **142** simultaneously provides boron enolate **143** and regenerates the ethyl(iodo)nickel species **140**. *Syn* aldol addition of the boron enolate **143** to the aldehyde provides the major aldol product **137**. It can be seen from this mechanism that **140** is likely the active catalyst for the formation of the major aldol product **137**.

In 2008, our group reported developments with nickel-catalysed intramolecular reductive aldol reactions that complemented the earlier cobalt-catalysed work (*vide supra*).[45] It was found that cyclisation of α,β-unsaturated amides or esters tethered to ketones could also be achieved by $Ni(acac)_2$ in combination with Et_2Zn. The nickel catalyst not only functions in much the same capacity as the earlier cobalt-system,

but also promotes the reactions of substrates that are either completely inert to the cobalt system, or react with much lower efficiencies (Scheme 15).

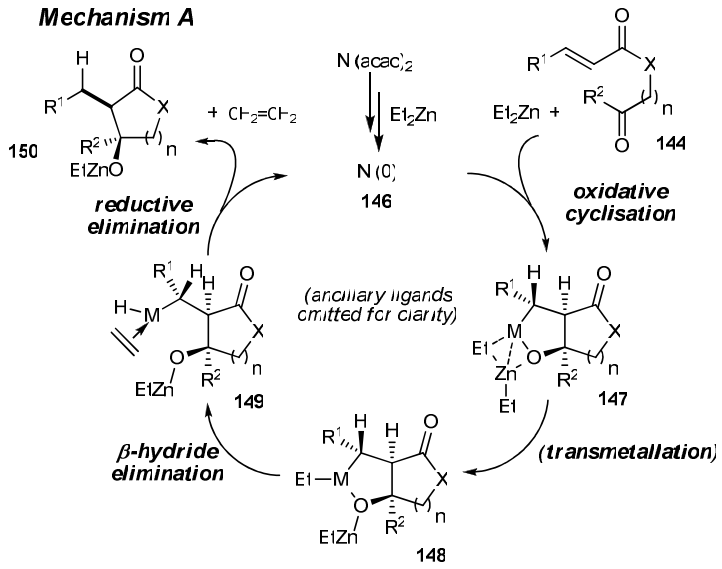


Scheme 15: Nickel-Catalysed Reductive Aldol Cyclisations Furnishing β-Hydroxylactones and Lactams

None of the lactam and lactone products illustrated in Scheme 15 would cyclise under the previous $Co(acac)_2 \cdot 2H_2O$ conditions.[43] $Ni(acac)_2$ was particularly adept at inducing cyclisation for substrates with heavy substitution at the α,β-unsaturated component of the starting substrates.

A mechanistic investigation was performed, in order to better understand this complex system. First, the oxidation state of the active nickel catalyst was established by performing the reaction with $Ni(cod)_2$ in place of $Ni(acac)_2$. It was assumed the active oxidation state of nickel in these reactions is zero, and that the Ni(0) species is generated by the well known reduction of $Ni(acac)_2$ with Et_2Zn.[46] However, with $Ni(acac)_2$ as the precatalyst, it is conceivable that the active catalyst is actually a Ni(II) species. In the event, cyclisation was observed with $Ni(cod)_2$, supporting the assumption that a Ni(0) species is the active catalyst.

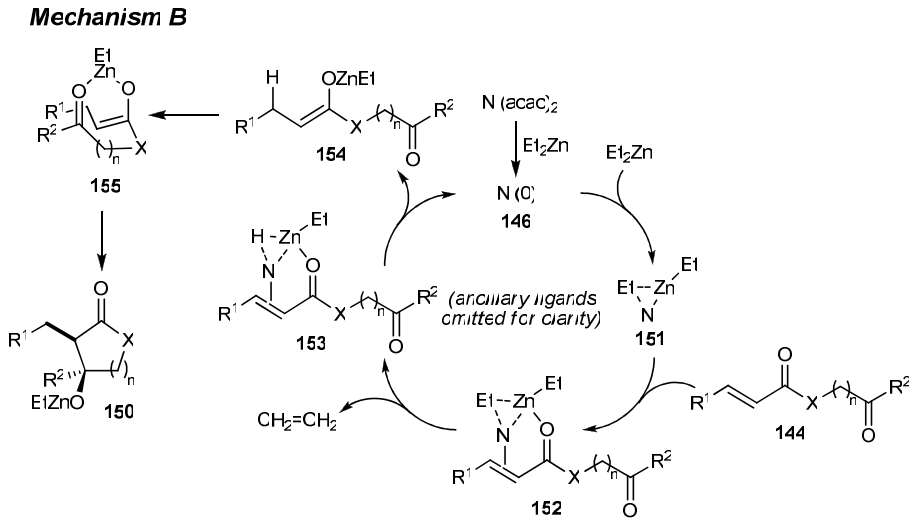
Based on the identification that Ni(0) is the active catalyst, two mechanisms seemed plausible. The first mechanism (mechanism A) is based on metallacycle participation (Scheme 16).



Scheme 16: Proposed Reaction Mechanism Invoking Metallacycle Participation

Oxidative cyclisation of Ni(0) (**146**) with the alkene and the ketone of the substrate **144** would result in metallacycle **147**. Cleavage of the metallacycle by transmetallation would provide nickel–ethyl species **148**, which then undergoes β-hydride elimination to generate metal hydride **149**. Reductive elimination of **149** provides zinc alkoxide **150** which is then protonated on workup to provide the aldol product **145**. Ethylene is also generated along with Ni(0) which then re-enters the catalytic cycle. The relative stereochemistries of the major diastereomers obtained in these reactions may be explained by the preference for formation of the bicyclic metallacycle **147** with a *cis*-ring junction, as opposed to the likely higher energy *trans*-ring junction.

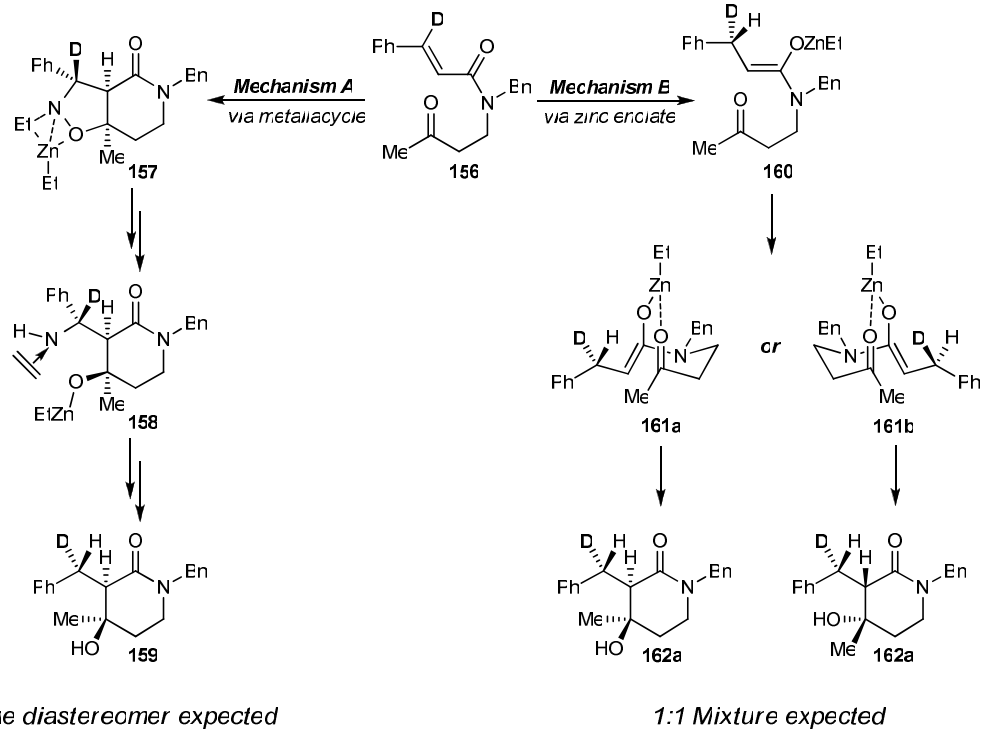
A second, alternative mechanism (mechanism B) that involves discrete enolate intermediates was also proposed (Scheme 17).



Scheme 17: Proposed Reaction Mechanism Invoking Zinc Enolate Formation

Interaction of Ni(0) (**146**) with Et_2Zn may lead to intermediate **151**, containing a three-centre-two-electron bridging interaction. Coordination of **151** to the substrate **144** would then provide **152**, which can undergo β-hydride elimination to provide metal hydride **153**. It is then possible for **153** to reorganise to yield zinc enolate **154**, which would undergo aldol cyclisation to **150**. The formation of **154** also provides Ni(0) (**146**) which can re-enter the catalytic cycle. The observed stereochemical outcome of the reactions may be explained by preferential formation of the *Z*-zinc enolate **154**, along with a chelated Zimmerman–Traxler-type transition state **155**.[47]

In an attempt to discriminate between mechanisms A and B, deuterium-labelled substrates were cyclised and the stereochemical outcome of the products analysed (Scheme 18).



Scheme 18: Expected Stereochemical Outcomes of Reductive Cyclisation of Deuterium-Labelled Substrate 156 Under Mechanisms A and B

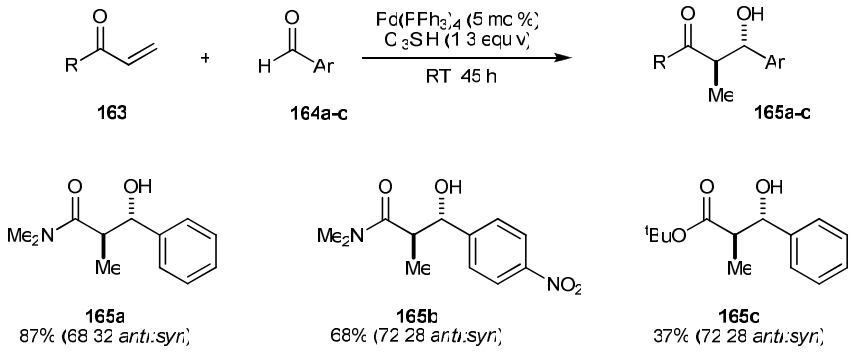
If metallacycle-based mechanism A (Scheme 16) is operative, then metallacycle **157** would be provided with the relative stereochemistry shown. Subsequent reductive elimination of nickel hydride **158** would lead to the formation of only one diastereomer **159**. If on the other hand, mechanism B (Scheme 17) is operative, then the reaction would proceed via zinc enolate **160** and should result in an observed product diastereomeric ratio of 1:1. This is because the mechanism proceeds via two Zimmerman–Traxler-type *trans* states **161a** and **161b** which should have almost identical energies, differing only by virtue of the deuterium label.

In the event, cyclisation of deuterium-labelled **157** resulted in an observed diastereomeric ratio of 1:1.3, determined by ^{1}H NMR spectroscopy. This outcome, which includes elements of both mechanisms, suggests that the true mechanism may be appreciably more complex, and that mechanisms A and B are an oversimplification of the true reaction pathway.

1.5 Palladium- Indium- and Iridium-Catalysed Reductive Aldol Reactions

1.5.1 Palladium-Catalysed Reductive Aldol Reactions

In 1998, Kiyooka and co-workers reported a palladium-catalysed reductive aldol reaction between α,β-unsaturated esters or amides and aldehydes (Scheme 19).[48]



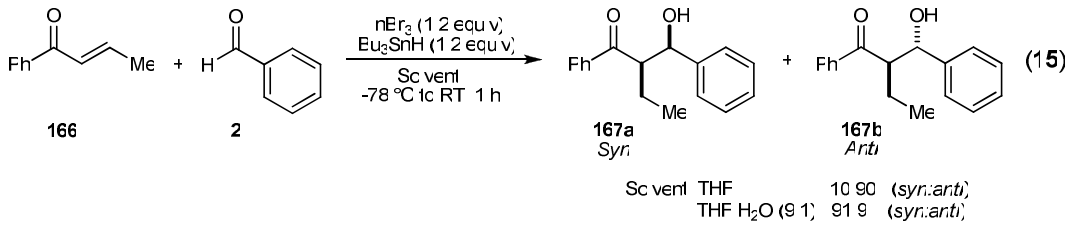
Scheme 19: Palladium-Catalysed Reductive Aldol Reactions Between Aryl Aldehydes and α,β-Unsaturated Carbonyl Compounds

Although this methodology is limited to aryl aldehydes, and produces low levels of diastereoselectivity, the reaction is of particular note for two reasons: i) it was the first reductive aldol reaction to be catalysed by a metal other than rhodium ii) it was the first reductive aldol reaction to exhibit *anti* selectivity. Kiyooka speculated that the mechanism may proceed via oxidative addition of trichlorosilane, rather than via a palladium enolate due to the observed *anti* selectivity.

1.5.2 Indium-Catalysed Reductive Aldol Reactions

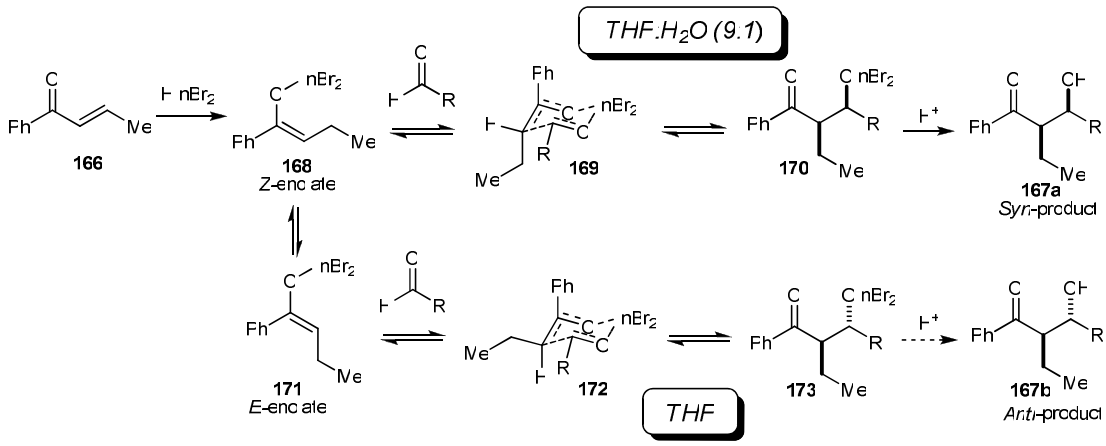
In 1998, Baba and co-workers described a new dichloroindium hydride species, generated by transmetallation between Bu_3SnH and $InCl_3$ forming Cl_2InH.[49] Baba went on to use this indium hydride to reduce acid chlorides to aldehydes.[50] The

reduction of α,β-unsaturated ketones was also investigated and during the course of these studies, it was found that the predominant reaction was a 1,4-reduction of the ketone by Br_2InH forming an enolate which then reacted with an aldehyde in a reductive aldol reaction (Eq 15).[51]



(15)

It was found that the reaction selectivity possessed a remarkable dependence on solvent. If the reaction was performed in THF, then the predominant stereoisomer was the *anti* diastereomer. When the solvent was changed to THF:H_2O (9:1), the *syn* diastereomer became the major stereoisomer. In order to explain this solvent dependency, a reversible mechanism was proposed (Scheme 20).



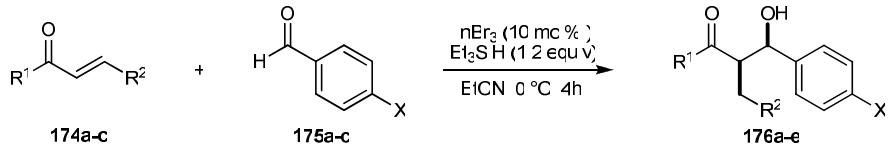
Scheme 20: Proposed Mechanism Explaining Solvency Dependence

Conjugate reduction of **166** by $HInBr_2$ initially results in the formation of the *Z*-enolate **168** due to the kinetically controlled 1,4-addition of indium hydride to the *cis* form of the enone. Enolate **168** can then react with the aldehyde to produce the *syn*-indium aldolate **170** via a Zimmerman-Traxler transition state **169**. When the reaction is performed in an aqueous medium, **170** is immediately protonated to yield the *syn*-product **167a**. If however, the reaction is performed in anhydrous THF, this

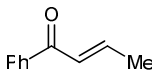
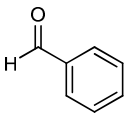
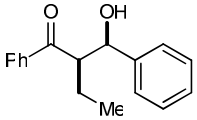
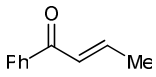
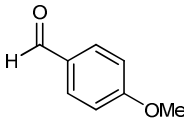
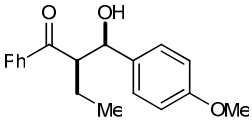
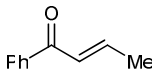
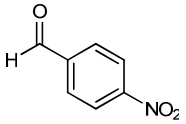
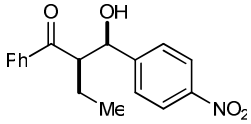
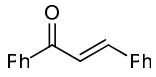
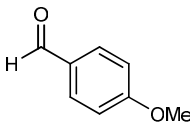
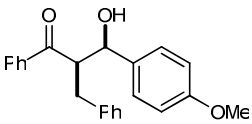
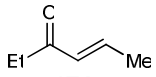
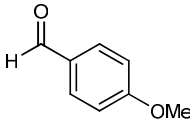
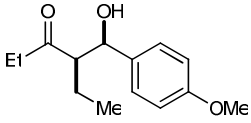
final step is prevented from taking place. The step from **168** to **170** is reversible and so the retro aldol reaction from **170** gives **168**. Now under thermodynamic conditions, the *E*-enolate **171** can form and then react with the aldehyde to produce the *anti*-aldolate **173**. On work-up, **173** is hydrolysed by water, yielding the *anti*-aldol product **167b**.

Baba and co-workers further developed their indium-mediated reductive aldol chemistry by developing an indium-catalysed reaction that did not rely on the preformation of Br_2InH or the use of $n Bu_3SnH$. Since many reductive aldol reactions had used a transition metal salt combined with a silane to produce an active metal-hydride species, Baba sought to do the same using $InBr_3$ together with Et_3SiH.[52] After some initial optimisation, the reaction of enones with aromatic aldehydes was realised (Table 24).

Table 24: Indium-Catalysed Reductive Aldol Reaction Using Et_3SiH as Stoichiometric Reductant



174a-c + 175a-c → 176a-e

Entry	Enone	Aldehyde	Product	Yield (%)	dr (*syn: anti*)
1	 **174a**	 **175a**	 **176a**	78	92:8
2	 **174a**	 **175b**	 **176b**	75	90:10
3	 **174a**	 **175c**	 **176c**	59	>99:1
4	 **174b**	 **175b**	 **176d**	82	>99:1
5	 **174c**	 **175b**	 **176e**	61	>99:1

The reaction proceeds in good yields with high levels of *syn*-selectivity. Aldehydes with electron donating groups on the aromatic ring tended to be higher yielding compared with electron-deficient aldehydes (Entry 2 vs 3). In addition, aromatic enones generally gave higher yields as compared to aliphatic enones (Entries 4 vs 5).

1.5.3 Iridium-Catalysed Reductive Aldol Reactions

In 2001, Morken and co-workers described the first and only iridium-catalysed reductive aldol reaction. As described earlier in this chapter, Morken had conducted an arrayed catalyst evaluation using glass 96-well plates. From this work, another system that would catalyse the reaction between methyl methacrylate and

acetophenone was identified.[53] It was found that using $[(cod)IrCl]_2$ and *i*-Pr-pybox as a one metal-ligand combination would effect the enantioselective reductive aldol reaction (1:1 *syn:anti*, 24% ee *anti*, 12% ee *syn*). Optimisation of these conditions with various ligands resulted in a new system that combined $[(cod)IrCl]_2$, Et_2MeSiH, and the aminoindanol-derived indane-pybox **177** (Figure 2).

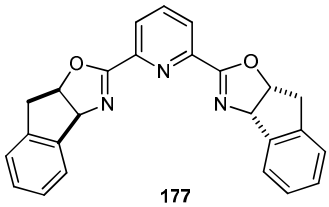
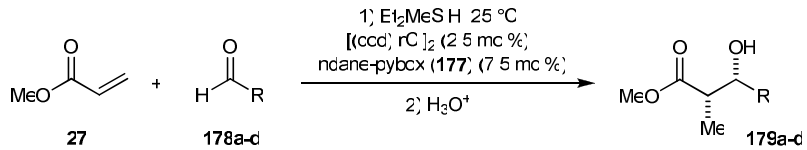
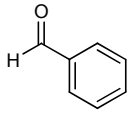
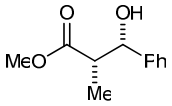
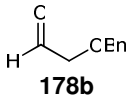
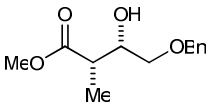
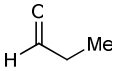
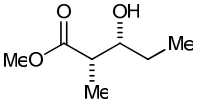
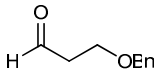
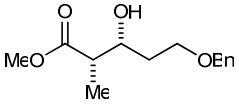


Figure 2: Indane-pybox ligand

With these conditions in hand, the reaction between methyl acrylate (**27**) and various aldehydes was examined (Table 25).

Table 25: Iridium-Pybox-Catalysed Asymmetric Reductive Aldol Reaction



Entry	Aldehyde	Product	Yield (%)	d.r. (syn:anti)	ee (%)[a]
1	 **178a**	 **178**	68	6.6:1	94
2	 **178b**	 **178b**	59	9.9:1	96
3	 **178c**	 **178c**	<5	n.a.	n.a.
4	 **178d**	 **178d**	65	2.7:1	82

a) ee of *syn* isomer

Aromatic aldehydes (entry 1) as well as α- or β-alkoxyaldehydes (entries 2 and 4) reacted readily with methyl acrylate to give aldol products in moderate yields, low to good diastereoselectivity, and excellent enantioselectivity. Aliphatic aldehydes were not such good substrates and failed to provide aldol products in isolable yield (Entry 3).

1.6 Lewis Base-Catalsyed Reductive Aldol Reactions

In 2008, Sugiura and co-workers disclosed an example of a reductive aldol reaction that does not use a transition-metal catalyst.[54] The reaction uses Lewis bases such as $Ph_3P{=}O$ and HMPA to effect reaction between α,β-unsaturated ketones and aldehydes in reasonable yields of 40-80% and with very high diastereoselectivity. The reaction as rendered asymmetric by the use of the chiral ligand BINAPO.

1.7 Conclusions

After its initial discovery in 1987 by Revis and Hilty, the reductive aldol reaction did not receive significant attention through the 1990's. This may have been because at first, the scope of the reaction was very narrow, and minimal diastereoselectivities were observed. However, in the last 10 years, improvements in the levels of diastereoselectivity, the use of new metals as catalysts, and the first enantioselective variants have demonstrated the true value of this important class of aldol reaction. The area continues to develop, and there are still challenges ahead, especially with regard to developing systems that encompass a broad substrate scope combined with consistently high levels of diastereoselectivity.

Our research group was the first to develop an enantioselective intramolecular reductive aldol reaction catalysed by copper. Subsequent work with nickel and cobalt broadened the substrate scope considerably and improved the yields although all the reaction were racemic. The development of the intermolecular reductive aldol reaction, catalysed by cobalt, will be the subject of chapters 2 and 3.

1.8 References

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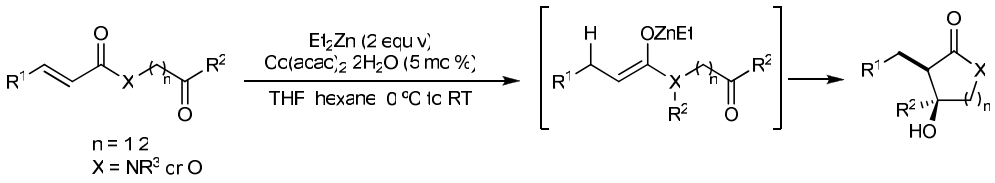
2 Racemic Cobalt-Catalysed Reductive Aldol Reactions[i]

2.1 Introduction

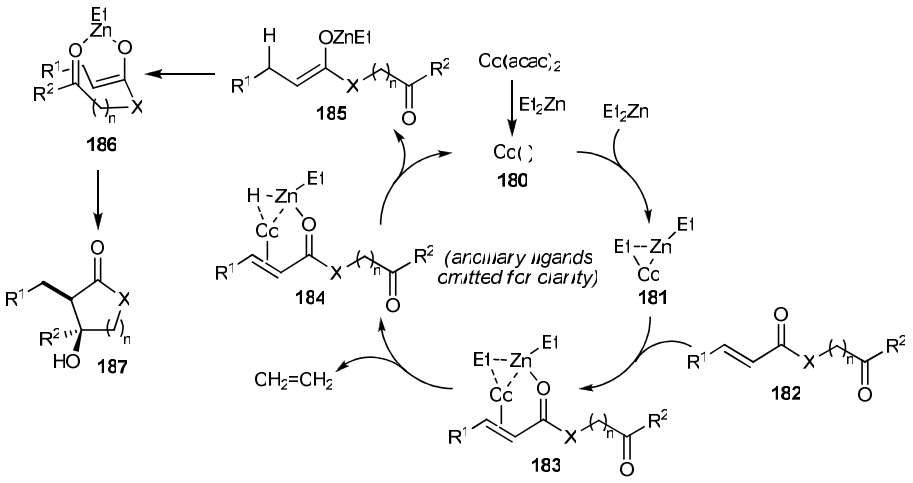
Previously in the Lam group, efforts had been directed towards the development of cyclisation methodology targeted towards the synthesis of β-hydroxylactones and lactams, by means of the reductive aldol reaction. Initial investigations used copper as the catalyst and TMDS as the stoichiometric reductant.[55] Limitations with this methodology invoked further research which led to the discovery that using $Co(acac)_2$ or $Ni(acac)_2$ in combination with Et_2Zn greatly enhanced the scope and potency of this methodology. Subsequently, both $Co(acac)_2$[56] and $Ni(acac)_2$[57] were used to expand upon the earlier copper-catalysed cyclisations to develop highly selective methodology for the synthesis of β-hydroxylactones and lactams (Scheme 21).



Scheme 21: Diastereoselective Intramolecular Reductive Aldol Cyclisations

This improved methodology, using either $Co(acac)_2$ and $Ni(acac)_2$, allowed access to an increased range of five- and six-membered β-hydroxylactones and lactams. A possible mechanism for the formation of the cyclised products, involving discrete enolate intermediates was proposed (Scheme 22).

[i] The work in this chapter was done in collaboration with Pekka M. Joensuu

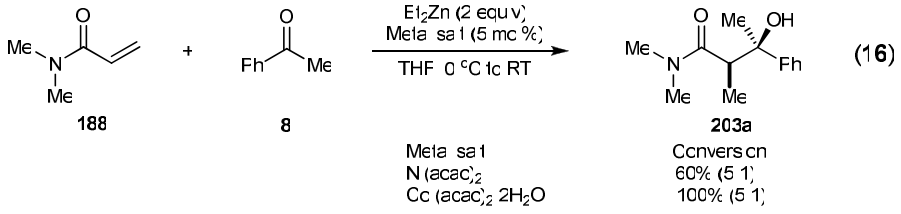


Scheme 22: Proposed Reaction Mechanism Invoking Zinc Enolate Formation

The zinc enolate **185** can react with the tethered ketone component to provide reductive aldol product **187**. It was postulated that in a suitably modified substrate, a zinc enolate might be trapped by a ketone electrophile in an *inter*molecular version of the reaction. There are far fewer examples of intermolecular reductive aldol reactions with ketone electrophiles compared to those with aldehydes. However, the use of a ketone allows access to tertiary alcohols, structural units that are present in numerous biological molecules.

2.2 Results and discussion

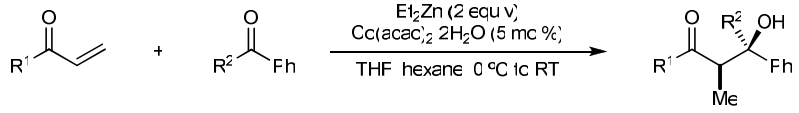
Initial investigations were conducted using commercially available *N,N*-dimethyl acrylamide (**188**) and acetophenone (**8**). Conditions were chosen that had already proved viable in the intramolecular reactions. Therefore both $Co(acac)_2 \cdot 2H_2O$ and $Ni(acac)_2$ were screened as catalysts in the presence of Et_2Zn as the stoichiometric reductant (Eq 16).

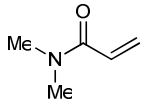
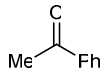
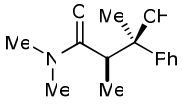
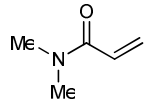
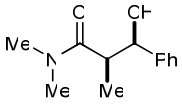
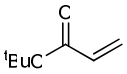
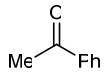
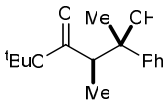
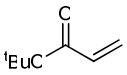
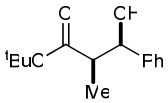


(16)

Although the use of both nickel and cobalt produced the desired aldol product **203a**, the use of cobalt resulted in a full conversion of starting materials. With these optimised conditions in hand, the versatility of the reaction in terms of substrate scope was examined. Reactions were performed using commercially available *N,N*-dimethyl acrylamide (**188**) and *t*-butyl acrylate (**135**) as the pro-nucleophile. Both acetophenone (**8**) and benzaldehyde (**2**) were chosen as the electrophilic partner (Table 26).

Table 26: Screening of Different Nucleophilic and Electrophilic Substrates



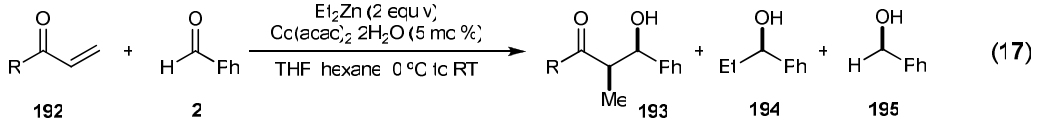
Entry	Amide / Ester	Electrophile	Product	Conversion[b]	dr[b]
1[a]	 **188**	 **8**	 **203a**	100%	5:1
2	 **188**	 **2**	 **189**	~ 50%	-
3	 **135**	 **8**	 **190**	100%	1:1
4	 **135**	 **2**	 **191**	~50%	-

a) Stereochemistry of product determined by comparison to literature data.[58] Stereochemistry of entry 2 product assigned by analogy b) Determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

N,N-dimethyl acrylamide (**188**) underwent smooth reductive aldol reaction with acetophenone (**8**) in 100% conversion and with 5:1 *syn* diastereoselection (entry 1). Reaction of *N,N*-dimethyl acrylamide (**188**) with benzaldehyde (**2**) resulted in incomplete conversion of the amide, and gave a complex mixture of products (entry 2). Reaction of *t*-butyl acrylate (**135**) with acetophenone (**8**) did result in smooth conversion to product, but with no diastereoselectivity (entry 3). Similar to the result in entry 2, the reaction between *t*-butyl acrylate (**135**) and benzaldehyde (**2**) also

resulted in incomplete conversion of the amide and a complex mixture of products was obtained (entry 4).

Reactions performed using benzaldehyde as the electrophile (entries 2 and 4) resulted in a complex mixture of products being obtained. Although some product was observed by ^{1}H NMR spectroscopy of the unpurified reaction mixture, the products of ethyl addition (**194**) and reduction (**195**) of the aldehyde were also observed (Eq 17).



(17)

Although these side reactions are also observed to a lesser degree in reactions with ketones, the higher electrophilicity of aldehydes makes the problem of reduction more significant.

The other observation to arise from the initial screening tests was the complete lack of diastereoselectivity observed when *t*-butyl acrylate (**135**) was used as a pro-nucleophile. A possible reason for this observation is illustrated in Figure 3.

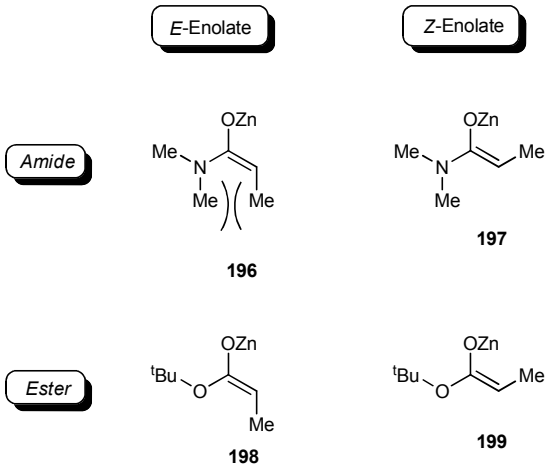


Figure 3: *Z*- and *E*-Enolates Showing 1,3-Allylic Strain in Amide *E*-Enolate

In the case of an *E*-amide enolate **196**, one of the N-methyl groups would come into close proximity with the methyl group on the double bond causing 1,3-allylic strain.[59] The Zimmerman–Traxler model[60] can be used to explain why the predomination of one enolate over another would lead to increased diastereoselectivity (Figure 4).

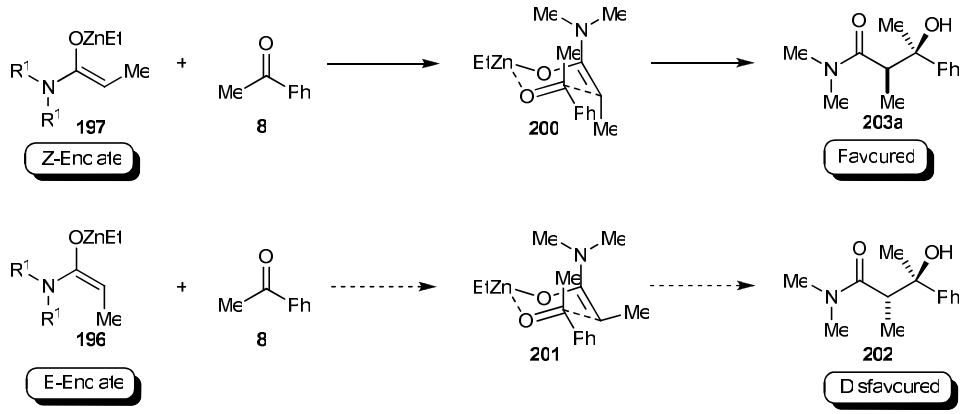
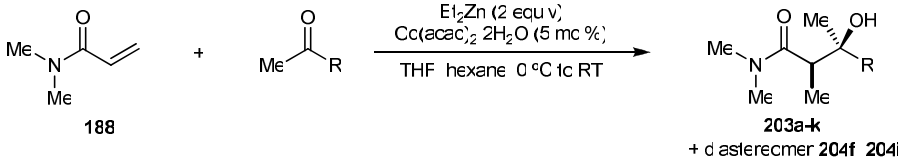


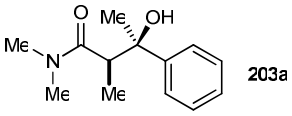
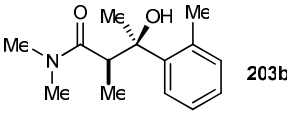
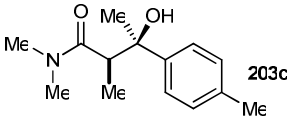
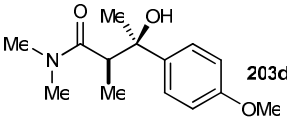
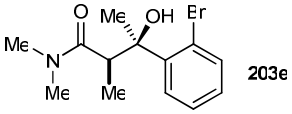
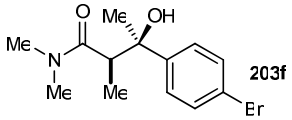
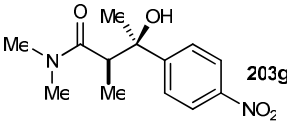
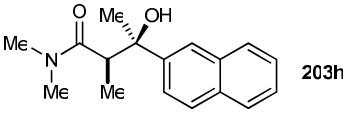
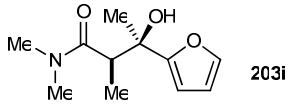
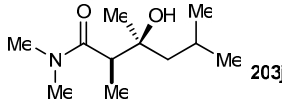
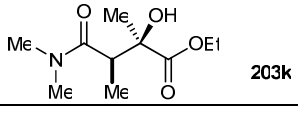
Figure 4: Zimmerman-Traxler Transition States to Explain Observed Diastereochemical Outcome

The predominant formation of the Z-amide enolate leads to the formation of **203a** over **202** in the observed diastereomeric ratio of 5:1 (entry 1, Table 24). In the case of the ester, the *t*-butyl group is able to adopt a position away from the methyl group in an *E*-enolate and so it can avoid a 1,3-interaction, allowing the formation of both the *E*- and the *Z*-enolates. This explanation may account for the lack of diastereoselectivity, which is observed when esters are used as nucleophiles (entry 3, Table 24).

The reaction of *N,N*-dimethyl acrylamide (**188**) with acetophenone (**8**) had resulted in smooth conversion to the desired reductive aldol product and therefore the reaction of α,β-unsaturated amides with ketones was chosen for further investigation. Initially, the reaction was performed with a range of aromatic and aliphatic ketones (Table 27).

Table 27: Reactions of *N,N*-Dimethyl Acrylamide with Ketones[a]



Entry	R	Product(s)	dr[b]	Yield(s)(%)[c]
1	Ph	 203a	5:1	75
2	2-MePh	 203b	9:1	68
3	4-MePh	 203c	5.5:1	75
4	4-MeOPh	 203d	6:1	84
5	2-BrPh	 203e	7:1	56
6	4-BrPh	 203f	3.5:1	73 (15)
7	4-NO_2Ph	 203g	-	0[d]
8	2-naphthyl	 203h	5:1	78
9	2-furyl	 203i	2.5:1	66 (25)
10	*i*-Bu	 203j	1:1	33
11	CO_2Et	 203k	-	0[d]

a) Reactions were conducted using 1.0 mmol of **188** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1–29 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated. d) A complex mixture of unidentified products was obtained.

N,N-dimethyl acrylamide (**188**) underwent reductive aldol reaction with a range of ketones to furnish products in yields of up to 78% and with diastereoselectivities of up to 9:1. Acetophenone derivatives containing methoxy, bromo, and alkyl substituents (entries 2-6) were all well tolerated under the standard reaction conditions. The exception was the strongly electron-withdrawing *para*-nitro acetophenone (entry 7), which resulted in the formation of a complex mixture of unidentified products. It is worth noting the beneficial effect that *ortho*-substitution had on the diastereoselectivity in the case of acetophenone derived substrates (entries 2 and 5). Unfortunantley the use of an aliphatic ketone resulted in no diastereoselectivity, although it did act as a competent substrate (entry 10). Reaction of ethyl pyruvate (entry 11) also resulted in only a complex mixture of unidentified products being formed. The relative stereochemistry of **203a** (entry 1) was determined by comparison with literature data.[58] In addition, an X-ray crystal of **203d** (entry 4) was obtained (Figure 5). The stereochemistry of the remaining aldol products was assigned by analogy.

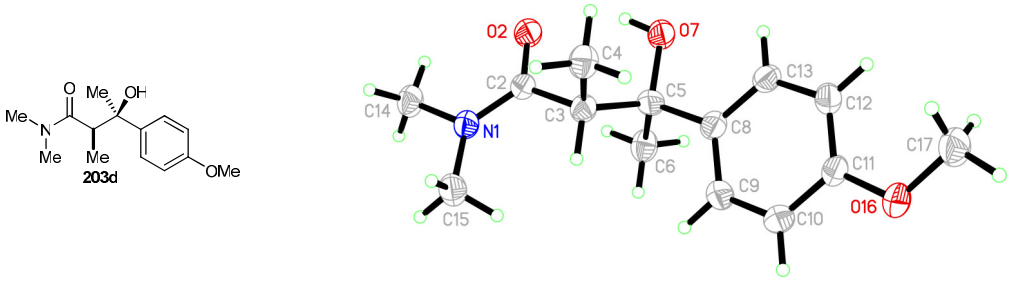
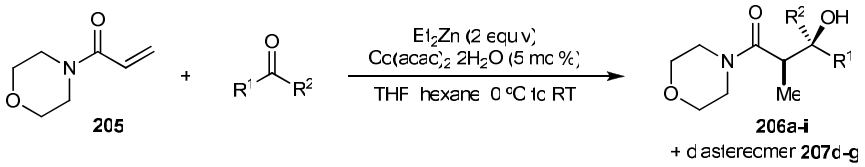
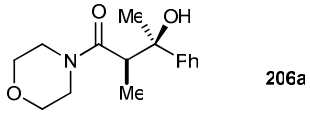
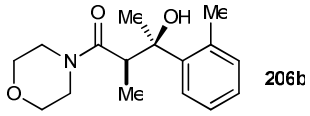
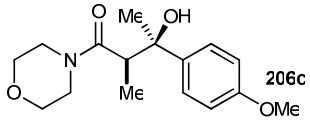
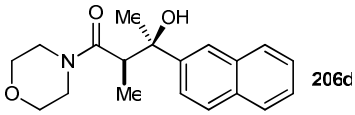
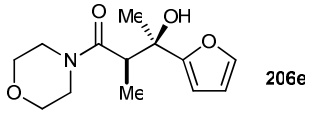
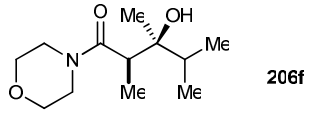
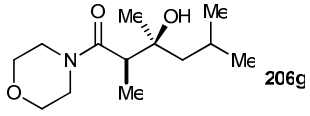
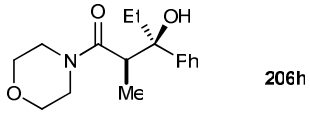
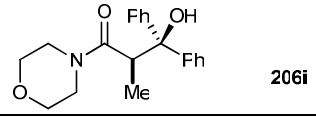


Figure 5: X-ray Crystal of 203d

To increase the utility of the methodology, a second series of reactions were performed employing 4-acryloylmorpholine (**205**) as the pro-nucleophile (Table 28).

Table 28: Reactions of 4-Acryloylmorpholine with Ketones[a]



Entry	R^1	R^2	Product(s)	dr[b]	Yield(s)(%)[c]
1	Me	Ph	 206a	5.5:1	80
2	Me	2-MePh	 206b	9:1	84
3	Me	4-MeOPh	 206c	6.5:1	85
4	Me	2-naphthyl	 206d	4.5:1	82 (17)
5	Me	2-furyl	 206e	3:1	72 (22)
6	Me	*i*-Pr	 206f	1:1	33 (31)
7	Me	*i*-Bu	 206g	1:1	35 (36)
8	Et	Ph	 206h	6:1	75
9	Ph	Ph	 206i	na	62

a) Reactions were conducted using 1.0 mmol of **205** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1–29 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) Isolated yield of major diastereomer. Numbers in parentheses refer to yields of minor diastereomers if isolated.

Reactions performed with 4-acryloylmorpholine (**205**) resulted in a similar pattern of results to those obtained with *N,N*-dimethyl acrylamide (**188**). However, both yield and diastereoselectivity were generally slightly higher (entries 1-5). Once again, reactions performed with aliphatic ketones (entries 6 and 7) yielded the desired products but with no diastereoselectivity. It was also possible to change the R^1

functionality to an ethyl group (entry 8), or a phenyl group (entry 9), where the presence of two bulky functionalities in close proximity did not hinder the reaction (entry 9). To determine the relative stereochemistry of the products, X-ray crystal structures of aldol products **206f** and **206g** were obtained (Figure 6). The stereochemistry of the remaining aldol products was assigned by analogy.

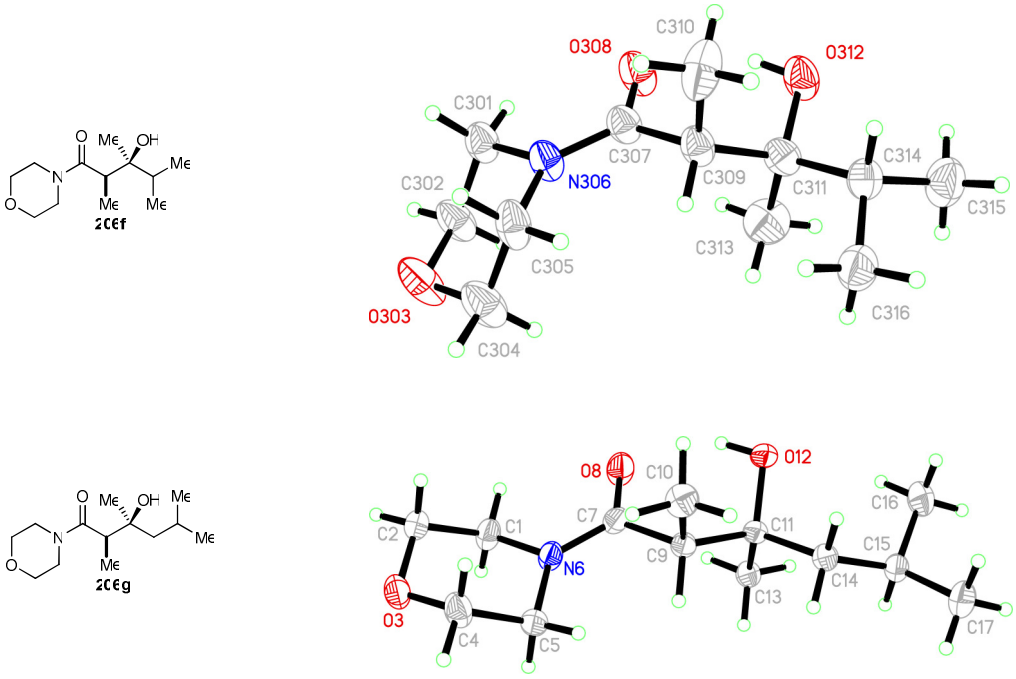
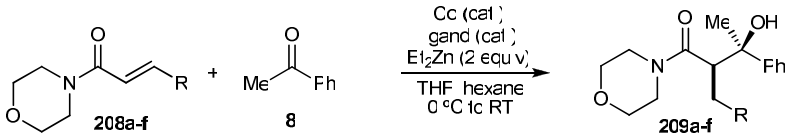


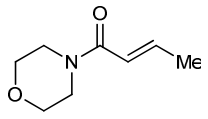
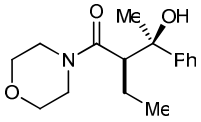
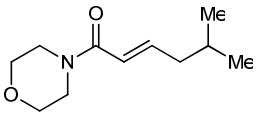
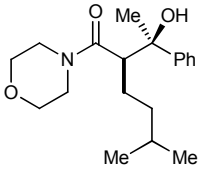
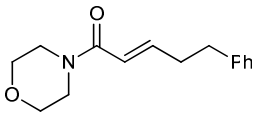
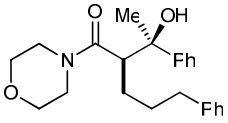
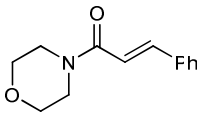
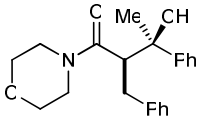
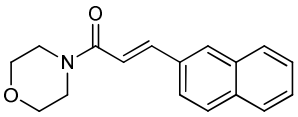
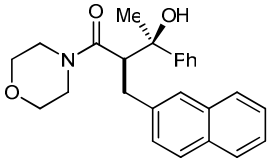
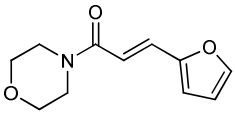
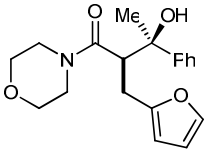
Figure 6: X-ray Crystals of Aldol Products 206f and 206g

The effect of substitution at the β-carbon of an α,β-unsaturated amide component was then explored. Reactions between various β-substituted 4-acryloylmorpholine substrates and acetophenone were carried out (Table 29). These reactions were performed by Pekka M. Joensuu.

Table 29:[i] Reactions of Acryloylmorpholine with Ketones[a]



Method A: Cc(acac)$_2$ 2H$_2$O (5 mc %)
Method B: CcC$_2$ (5 mc %), Cy$_2$FFh (5 5 mc %)

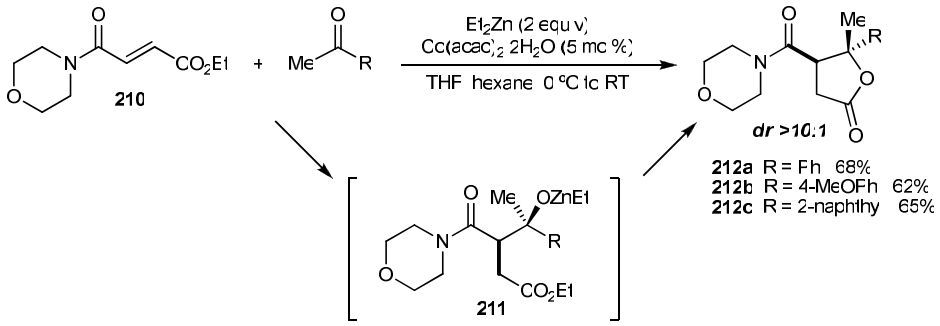
Entry	Method	Substrate	Product	dr[b]	Yield (%)[c]
1	B	 **208a**	 **209a**	>19:1	76
2	B	 **208b**	 **209b**	>19:1	85
3	B	 **208c**	 **209c**	16:1	81[d]
4	A	 **208d**	 **209d**	>19:1	71
5	A	 **208e**	 **209e**	10:1	74
6	A	 **208f**	 **209f**	9:1	84

a) Reactions were conducted using 1.0 mmol of **208a-f** and 1.1 mmol of acetophenone (**8**) in THF (10 mL) and hexane (2 mL) for 2–6 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) Isolated yield of major diastereomer. d) Yield of a 16:1 inseparable mixture of diastereomers.

[i] Reactions performed by Pekka M. Joensuu

The results in Table 29 clearly indicate the beneficial effects of substitution at the β-position of the unsaturated amide with an increase in diastereoselectivity of up to >19:1. Substitution with linear and branched alkyl groups (entries 1-2), as well as aromatic (entries 3-5) and heteroaromatic groups (entry 6) were tolerated. In the case of alkyl substituted morpholine amides, using $Co(acac)_2 \cdot 2H_2O$ as the pre-catalyst resulted in incomplete conversions. However, a combination of $CoCl_2$ and the electron-rich phosphine ligand Cy_2PPh delivered the desired products in much improved yields (entries 1-3).

As described previously, the α,β-unsaturated *t*-butyl acrylate **27** successfully underwent reaction with acetophenone but with no diastereoselectivity. Therefore the reaction of substrate **210** was of interest, since assuming it undergoes conjugate reduction, it has the possibility of forming products α- to the amide as well as α- to the ester. In the event, reaction of **210** with a range of methyl ketones resulted exclusively in the formation of lactones **212a-c**. These products form *via* cyclisation of the intermediate zinc alkoxide **211** onto the pendant ethyl ester in 62%-68% yield and with a diastereoselectivity of greater than 10:1, clearly demonstrating the preferential formation of an amide enolate, over an ester enolate (Scheme 23)[i].

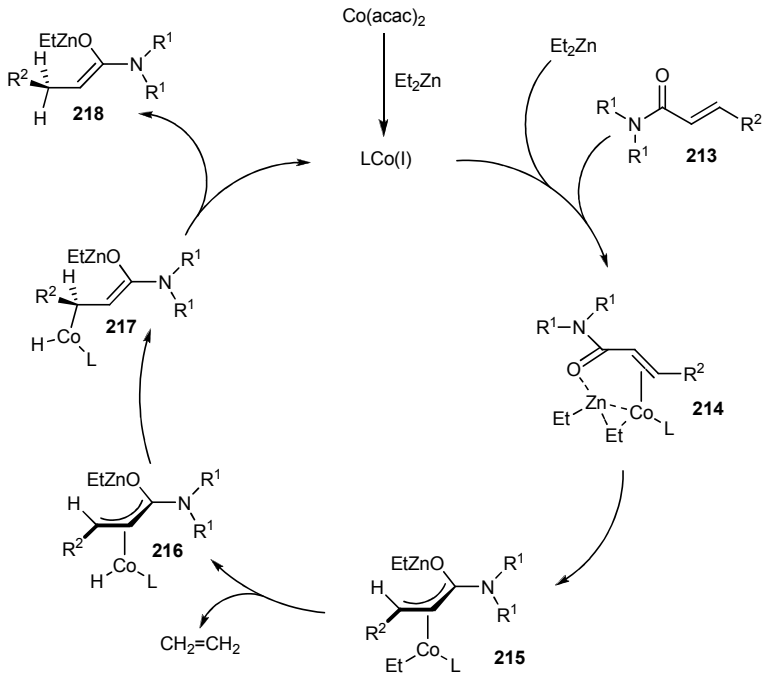


Scheme 23: Reductive Aldol Coupling of 210 with Various Ketones Producing Lactones.

The reactions versatility in terms of nucleophilic and electrophilic partners has been demonstrated and now a postulated mechanism for this novel catalytic system is presented.

[i] Reactions performed by Pekka M. Joensuu

Seminal work by MacKenzie and co-workers[61] along with important contributions by Ogoshi, Kurosawa and co-workers[62] has described the formation of π-allylmetal complexes in the presence of low-valent transition metals, α,β-unsaturated carbonyl compounds and a Lewis acid. Based on these findings, a possible mechanism for the reaction is presented in Scheme 24 and involves the participation of π-allylcobalt species.

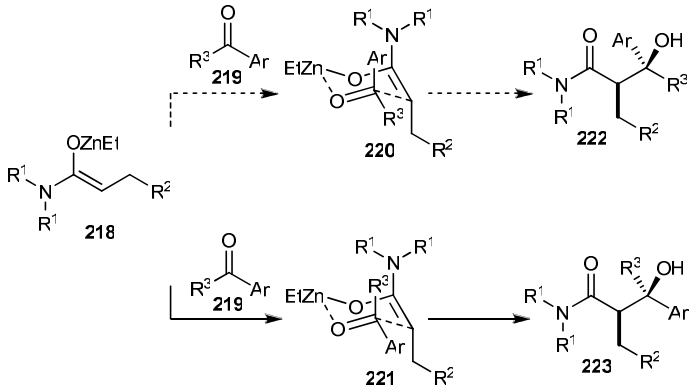


Scheme 24: Possible Catalytic Cycle

Treatment of $Co(acac)_2$ with Et_2Zn leads to the formation of a cobalt (I) species which, in the presence of excess Et_2Zn, can then bind with **213** to form metallacycle **214**. This type of three-centre-two-electron bridging interaction has precedent in studies conducted by Montgomery and co-workers in related nickel-catalysed reactions.[63] In addition, these types of complexes have been observed crystallographically in the case of cobalt[64] and nickel[65] involving Grignard[63,64a] and organolithium[64b] reagents. Oxidative addition of Co(I) into the α,β-unsaturated amide of **214** and transmetallation of an ethyl group from zinc to cobalt results in the formation of π-allylcobalt species **215** which can then undergo β-hydride elimination

to form cobalt hydride **216**. This is followed by a η^3-η^1 isomerisation to produce **217** which reductively eliminates to provide the *Z*-zinc enolate **218** and regenerate the Co(I) species. The enolate **218** now undergoes aldol reaction with the ketone. This model also explains the earlier observation illustrated in Scheme 23 where an amide enolate formed preferentially over an ester enolate. This is due to the greater Lewis basicity of the amide, resulting in regiochemical binding of Et_2Zn/Co at the amide carbonyl of **210** (Scheme 23) rather than at the ester carbonyl.

The diastereochemical outcomes of these reactions may be explained by the Zimmerman–Traxler model[60] involving the participation of *Z*-zinc enolate **218** in a chair-like transition state. In this model, the larger aromatic substituent of the ketone prefers to reside in a less sterically hindered pseudoequatorial position, compared to a pseudoaxial position (Scheme 25). This could also explain the lack of selectivity observed with aliphatic ketones where the difference in size between the two substituents on the carbonyl is presumably too small to give rise to appreciable diastereoselectivity.



Scheme 25: Model for Stereochemical Outcome

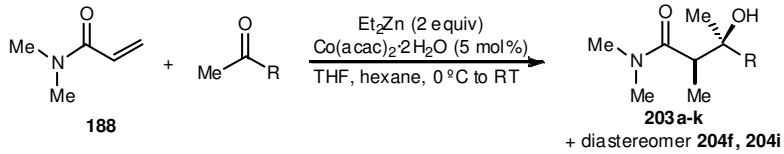
2.3 Conclusions

Cobalt-catalysed conjugate reduction of readily accessible α,β-unsaturated amides using Et_2Zn as the stoichiometric reductant generates zinc enolates which can engage in efficient aldol couplings to ketones, providing tertiary β-hydroxycarbonyl compounds in high yields and with good diastereoselectivity. Advantages of this method include its scalability, operation under ambient temperatures, and its allowance for significant variation of the α-substituent in the products. The highest yields and diastereoselectivities were obtained with aromatic ketones such as acetophenone and its derivatives. Unfortunately, although aliphatic ketones were found to undergo the reductive aldol reaction, no diastereoselection was observed.

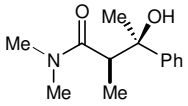
2.4 Experimental

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. All commercially available reagents were used as received. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[66] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX500 (500 MHz) spectrometer, a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), m (multiplet), app (apparent). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound.

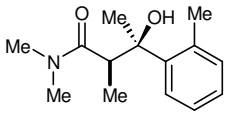
Reductive Aldol Reactions Using *N*,*N*-Dimethylacrylamide: General Procedure A



To a solution $Co(acac)_2{\cdot}2H_2O$ (12.9 mg, 0.05 mmol), *N,N*-dimethylacrylamide (**188**) (103 μL, 1.00 mmol) and the appropriate ketone (1.10 mmol) in THF (10 mL) at 0 °C was added Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) dropwise over 1 min. The reaction was stirred at 0 °C until complete consumption of the acrylamide as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (3 mL) and the resulting mixture was stirred for 15 min. Further saturated aqueous NH_4Cl solution (30 mL) was added, and the mixture was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the aldol product(s).

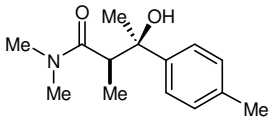


(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-phenylbutanamide (203a). The title compound was prepared according to General Procedure A from acetophenone (127 μL, 1.10 mmol) for a reaction time of 2 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (166 mg, 75%) that displayed spectral data consistent with those reported previously.[57]

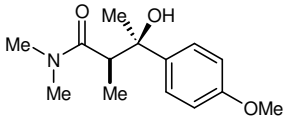


(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-(2-methylphenyl)butanamide (203b). The title compound was prepared according to General Procedure A from 2′-methylacetophenone (144 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (157 mg, 68%). m.p. 61-63 °C; IR ($CHCl_3$) 3324 (OH), 2973, 2934, 1619 (C=O), 1463, 1415, 1399, 1059, 765, 729 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.23-7.11 (3H, m, Ar**H**), 6.01 (1H, br s, O**H**), 3.38 (1H, q, *J* = 7.0 Hz, $CH_3C\mathbf{H}$), 3.17 (3H, s, $NC\mathbf{H}_3$), 3.05 (3H, s, $NC\mathbf{H}_3$), 2.53 (3H, s, $ArC\mathbf{H}_3$), 1.61 (3H, s, $C\mathbf{H}_3COH$),

0.94 (3H, d, J = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.7 (C), 143.4 (C), 133.4 (C), 132.3 (CH), 127.1 (CH), 126.6 (CH), 125.8 (CH), 75.7 (C), 41.1 (CH), 37.6 (CH_3), 35.6 (CH_3), 28.9 (CH_3), 22.8 (CH_3), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{21}NO_2Na$ $[M+Na]^+$: 258.1465, found: 258.1466.

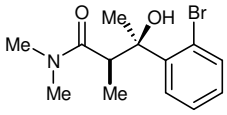


(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-(4-methylphenyl)butanamide (203c). The title compound was prepared according to General Procedure A from 4'-methylacetophenone (147 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (186 mg, 79%). m.p. 112-114 °C; IR ($CHCl_3$) 3336 (OH), 2973, 2932, 1619 (C=O), 1513, 1461, 1415, 1072, 821 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35 (2H, d, J = 8.1 Hz, Ar**H**), 7.16 (2H, d, J = 8.1 Hz, Ar**H**), 5.87 (1H, br s, O**H**), 3.15 (3H, s, NC**H**$_3$), 3.05 (3H, s, NC**H**$_3$), 2.99 (1H, q, J = 7.1 Hz, CH$_3$C**H**), 2.35 (3H, s, ArC**H**$_3$), 1.51 (3H, s, C**H**$_3$COH), 0.89 (3H, d, J = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.8 (C), 143.0 (C), 135.9 (C), 128.7 (2 x CH), 124.8 (2 x CH), 74.6 (C), 43.8 (CH), 37.7 (CH_3), 35.5 (CH_3), 30.1 (CH_3), 21.0 (CH_3), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$: 236.1645, found: 236.1646.



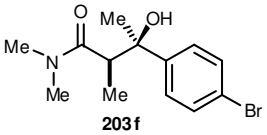
(±)-(2*R*,3*R*)-3-Hydroxy-3-(4-methoxyphenyl)-*N*,*N*,2-trimethylbutanamide (203d). The title compound was prepared according to General Procedure A from 4'-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (212 mg, 84%). Slow evaporation of a hexane solution of **5d** provided colourless crystalline crystals that were suitable for X-ray crystallography. m.p. 108-110 °C; IR ($CHCl_3$) 3336 (OH), 2971, 2934, 1616 (C=O), 1513, 1461, 1416, 1397, 1247, 1176 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39 (2H, dm, J = 9.0 Hz, Ar**H**), 6.89 (2H, dm, J = 9.0 Hz, Ar**H**), 5.87 (1H, br s, O**H**), 3.82 (3H, s, OC**H**$_3$) 3.15 (3H, s, NC**H**$_3$), 3.04 (3H, s, NC**H**$_3$), 2.96 (1H, q, J = 7.1 Hz, CH$_3$C**H**), 1.51 (3H, s, C**H**$_3$COH), 0.89 (3H, d, J = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.8 (C), 158.1 (C), 138.2 (C), 126.0 (2 x CH), 113.3 (2 x CH), 74.5 (C), 55.2 (CH_3), 43.9 (CH), 37.7 (CH_3), 35.5

(CH_3), 30.0 (CH_3), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{22}NO_3$ $[M+H]^+$: 252.1594, found: 252.1594.

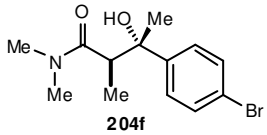


(±)-(2*R*,3*R*)-3-(2-Bromophenyl)-3-hydroxy-*N*,*N*,2-trimethylbutanamide (203e). The title compound was prepared according to General Procedure A from 2'-bromoacetophenone (148 μL, 1.10 mmol) for a reaction time of 29 h and purified by column chromatography (10% EtOAc/petrol) to give an off-white solid (169 mg, 56%). m.p. 74-76 °C; IR ($CHCl_3$) 3313 (OH), 2972, 2934, 1619 (C=O), 1460, 1419, 1399, 1313, 1015, 758 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.08-8.05 (1H, m, Ar**H**), 7.58-7.55 (1H, m, Ar**H**), 7.37-7.33 (1H, m, Ar**H**), 7.13-7.08 (1H, m, Ar**H**), 6.32 (1H, br s, O**H**), 4.21 (1H, q, *J* = 7.0 Hz, CH_3CH), 3.23 (3H, s, NCH_3), 3.06 (3H, s, NCH_3), 1.73 (3H, s, CH_3COH), 0.86 (3H, d, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.5 (C), 143.7 (C), 134.5 (CH), 129.7 (CH), 128.4 (CH), 127.4 (CH), 118.7 (C), 75.3 (C), 38.3 (CH), 37.6 (CH_3), 35.5 (CH_3), 26.9 (CH_3), 12.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{18}BrNO_2$ $[M+H]^+$: 300.0594, found: 300.0594.

(±)-(2*R*,3*R*)-3-(4-Bromophenyl)-3-hydroxy-*N*,*N*,2-trimethylbutanamide (203f) and (±)-(2*R*,3*S*)-3-(4-bromophenyl)-3-hydroxy-*N*,*N*,2-trimethylbutanamide (204f)



203f



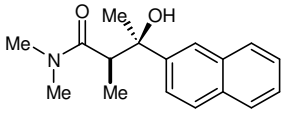
204f

General Procedure A was followed using 4'-bromoacetophenone (219 mg, 1.10 mmol) for a reaction time of 22 h and the reaction mixture was purified by column chromatography (20% EtOAc/petrol) to give the *aldol product* **203f** (207 mg, 73%) as an off-white solid followed by the *aldol product* **204f** (45 mg, 15%) as an off-white solid.

Data for **203f**: m.p. 98-100 °C; IR ($CHCl_3$) 3335 (OH), 2973, 2933, 1619 (C=O), 1489, 1461, 1415, 1399, 1074, 1009 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.7 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.7 Hz, Ar**H**), 5.97 (1H, br s, O**H**), 3.15 (3H, s,

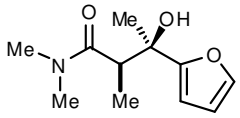
NC**H**$_3$), 3.05 (3H, s, NC**H**$_3$), 2.95 (1H, q, *J* = 7.0 Hz, CH$_3$C**H**), 1.50 (3H, s, C**H**$_3$COH), 0.87 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.4 (C), 145.1 (C), 131.1 (C), 126.9 (2 x CH), 120.4 (2 x CH), 74.5 (CH), 43.6 (CH), 37.7 (CH_3), 35.6 (CH_3), 29.8 (CH_3), 12.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{19}BrNO_2$ $[M+H]^+$: 300.0594, found: 300.0593.

Data for **204f**: m.p. 65-67 °C; IR ($CHCl_3$) 3337 (OH), 2936, 1617 (C=O), 1483, 1394, 1306, 1089, 1008, 930, 823 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.7 Hz, Ar**H**), 7.28 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.10 (1H, s, O**H**), 3.13 (1H, q, *J* = 7.0 Hz, CH$_3$C**H**), 2.86 (3H, s, NC**H**$_3$), 2.67 (3H, s, NC**H**$_3$), 1.42 (3H, s, C**H**$_3$COH), 1.34 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.8 (C), 148.1 (C), 131.0 (2 x CH), 126.4 (2 x CH), 120.3 (C), 74.6 (C), 43.0 (CH), 37.2 (CH_3), 35.1 (CH_3), 27.2 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{19}BrNO_2$ $[M+H]^+$: 300.0594, found: 300.0592.

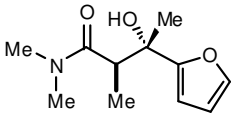


(±)-(2*R*,3*R*)-3-Hydroxy-*N*,*N*,2-trimethyl-3-naphthalen-2-ylbutanamide (203h). The title compound was prepared according to General Procedure A from 2-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (212 mg, 78%). m.p. 112-114 °C; IR ($CHCl_3$) 3334 (OH), 2973, 2933, 1618 (C=O), 1457, 1416, 1398, 1182, 1129, 748 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.05 (1H, s, Ar**H**), 7.90-7.87 (1H, m, Ar**H**), 7.85-7.82 (2H, m, Ar**H**), 7.51-7.46 (3H, m, Ar**H**), 6.08 (1H, br s, O**H**), 3.20 (3H, s, NC**H**$_3$), 3.14 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**), 3.08 (3H, s, NC**H**$_3$), 1.61 (3H, s, C**H**$_3$COH), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.6 (C), 143.2 (C), 133.2 (C), 132.2 (C), 128.2 (CH), 127.7 (CH), 127.4 (CH), 125.9 (CH), 125.6 (CH), 124.0 (CH), 123.1 (CH), 74.9 (C) 43.5 (CH), 37.7 (CH_3), 35.6 (CH_3), 30.0 (CH_3), 12.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found: 272.1646.

(±)-(2*R*,3*R*)-3-Furan-2-yl-3-hydroxy-*N*,*N*,2-trimethylbutanamide (203i) and (±)-(2*R*,3*S*)-3-furan-2-yl-3-hydroxy-*N*,*N*,2-trimethylbutanamide (204i)



203i



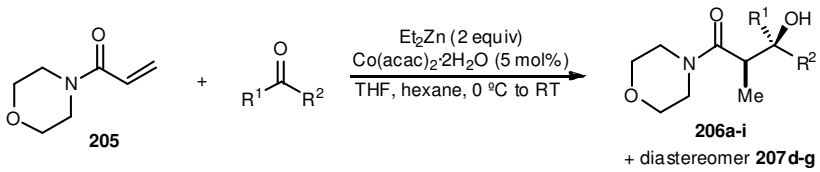
204i

General Procedure A was followed using 2-furyl methyl ketone (121 mg, 1.10 mmol) for a reaction time of 1 h and the reaction mixture was purified by column chromatography (20% EtOAc/petrol) to give *aldol product* **203i** (130 mg, 66%) as a white solid followed by *aldol product* **204i** (49 mg, 25%) as a colourless oil.

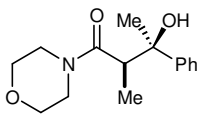
Data for **203i**: m.p. 78-80 °C; IR ($CHCl_3$) 3348 (OH), 2978, 2935, 1622 (C=O), 1461, 1399, 1154, 1076, 1002, 736 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.32 (1H, m, C**H**), 6.35-6.34 (2H, m, 2 x C**H**), 5.78 (1H, br s, O**H**), 3.14 (3H, s, NC**H**$_3$), 3.11 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 3.03 (3H, s, NC**H**$_3$), 1.52 (3H, s, C**H**$_3$COH), 0.98 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.2 (C), 157.8 (C), 140.8 (CH), 110.1 (CH), 105.2 (CH), 73.4 (C), 41.6 (CH), 37.6 (CH_3), 35.3 (CH_3), 27.8 (CH_3), 12.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{17}NO_3Na$ $[M+Na]^+$: 234.1101, found: 234.1103.

Data for **204i**: IR (film) 3409 (OH), 2989, 2938, 1619 (C=O), 1505, 1400, 1154, 1069, 938, 737 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.27 (1H, s, Ar**H**), 6.28 (1H, dd, *J* = 3.2, 1.9 Hz, Ar**H**), 6.21 (1H, dd, *J* = 3.2, 0.9 Hz, Ar**H**), 5.98 (1H, br s, O**H**), 3.23 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.94 (3H, s, NC**H**$_3$), 2.80 (3H, s, NC**H**$_3$), 1.47 (3H, s, C**H**$_3$COH), 1.28 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.0 (C), 161.0 (C), 140.7 (CH), 110.4 (CH), 104.2 (CH), 72.4 (C), 41.0 (CH), 37.2 (CH_3), 35.2 (CH_3), 24.9 (CH_3), 11.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$: 212.1281, found: 212.1281.

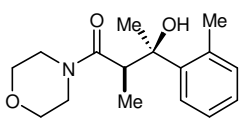
Reductive Aldol Reactions Using 4-Acryloylmorpholine: General Procedure B



To a solution $Co(acac)_2 \cdot 2H_2O$ (12.9 mg, 0.05 mmol), 4-acryloylmorpholine (126 μL, 1.00 mmol) and the appropriate ketone (1.10 mmol) in THF (10 mL) at 0 °C was added Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) dropwise over 1 min. The reaction was stirred at 0 °C until complete consumption of 4-acryloylmorpholine as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (3 mL) and the resulting mixture was stirred for 15 min. Further saturated aqueous NH_4Cl solution (30 mL) was added, and the mixture was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the aldol product(s).

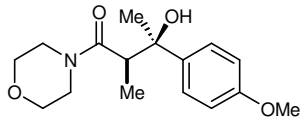


(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-1-morpholin-4-yl-3-phenylbutan-1-one (206a). The title compound was prepared according to General Procedure B from acetophenone (127 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (210 mg, 80%). m.p. 129-131 °C; IR ($CHCl_3$) 3366 (OH), 2971, 2928, 2856, 1614 (C=O), 1462, 1445, 1231, 1117, 1022 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48-7.45 (2H, m, Ar**H**), 7.39-7.33 (2H, m, Ar**H**), 7.27-7.22 (1H, m, Ar**H**), 5.66 (1H, br s, O**H**), 3.81-3.54 (8H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N), 2.96 (1H, q, *J* = 7.1 Hz, CH_3**C**$\mathbf{H}$), 1.55 (3H, s, **C**$\mathbf{H}_3$COH), 0.91 (3H, d, *J* = 7.1 Hz, **C**$\mathbf{H}_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.0 (C), 145.7 (C), 127.9 (2 x CH), 126.4 (CH), 124.8 (2 x CH), 74.6 (C), 66.8 (CH_2), 66.7 (CH_2), 46.2 (CH_2), 43.3 (CH), 41.8 (CH_2), 29.8 (CH_3), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1594, found: 264.1590.



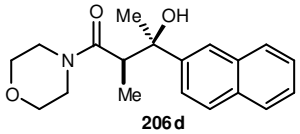
(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(2-methylphenyl)-1-morpholin-4-ylbutan-1-one (206b). The title compound was

prepared according to General Procedure B from 2′-methylacetophenone (144 μL, 1.10 mmol) for a reaction time of 4 h and purified by column chromatography (20% EtOAc/petrol) to give a colourless oil (231 mg, 84%). IR (film) 3349 (OH), 2972, 2928, 2856, 1614 (C=O), 1464, 1439, 1230, 1117, 1020 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = Hz, Ar**H**), 7.22-7.10 (3H, m, Ar**H**), 5.74 (1H, br s, O**H**), 3.81-3.55 (8H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N), 3.31 (1H, q, *J* = 7.0 Hz, CH_3**C**$\mathbf{H}$), 2.52 (3H, s, Ar**C**$\mathbf{H}_3$), 1.63 (3H, s, **C**$\mathbf{H}_3$COH), 0.96 (3H, d, *J* = 7.0 Hz, **C**$\mathbf{H}_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.0 (C), 143.1 (C), 133.5 (C), 132.4 (CH), 126.9 (CH), 126.7 (CH), 125.7 (CH), 75.8 (C), 66.8 (CH_2), 66.7 (CH_2), 46.3 (CH_2), 42.0 (CH), 40.8 (CH_2), 28.9 (CH_3), 22.8 (CH_3), 13.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1750.

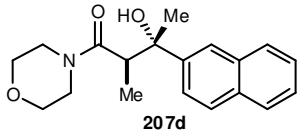


(±)-(2*R*,3*R*)-3-Hydroxy-3-(4-methoxyphenyl)-2-methyl-1-morpholin-4-ylbutan-1-one (206c). The title compound was prepared according to General Procedure B from 4′-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 6 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (249 mg, 85%). m.p. 77-79 °C; IR ($CHCl_3$) 3366 (OH), 2970, 2931, 2856, 1612 (C=O), 1513, 1464, 1246, 1232, 1117 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37 (2H, dm, *J* = 9.0 Hz, Ar**H**), 6.89 (2H, dm, *J* = 9.0 Hz, Ar**H**), 5.58 (1H, br s, O**H**), 3.82 (3H, s, O**C**$\mathbf{H}_3$) 3.79-3.53 (8H, m, 2 x O**C**$\mathbf{H}_2$**C**$\mathbf{H}_2$N), 2.90 (1H, q, *J* = 7.1 Hz, CH_3**C**$\mathbf{H}$), 1.53 (3H, s, **C**$\mathbf{H}_3$COH), 0.91 (3H, d, *J* = 7.1 Hz, **C**$\mathbf{H}_3$CH); δ 176.3 (C), 158.1 (C), 138.0 (C), 126.0 (2 x CH), 113.3 (2 x CH), 74.4 (C), 66.8 (CH_2), 66.7 (CH_2), 55.1 (CH_3), 46.3 (CH_2), 43.5 (CH), 41.9 (CH_2), 29.9 (CH_3), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_4$ $[M+H]^+$: 294.1700, found: 294.1700.

(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-1-morpholin-4-yl-3-naphthalen-2-ylbutan-1-one (206d) and (±)-(2*R*,3*S*)-3-hydroxy-2-methyl-1-morpholin-4-yl-3-naphthalen-2-ylbutan-1-one (207d).



206d



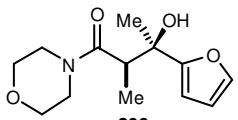
207d

General Procedure B was followed using 2-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 4 h and the reaction mixture was purified by column chromatography (20% EtOAc/petrol) to give the *aldol product* **206d** (255 mg, 82%) as a white solid followed by the *aldol product* **207d** (54 mg, 17%) as an off-white solid.

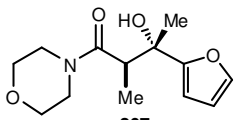
Data for **206d**: m.p. 97-99 °C; IR ($CHCl_3$) 3358 (OH), 2972, 2927, 2856, 1612 (C=O), 1468, 1437, 1231, 1117, 1026 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.04 (1H, s, Ar**H**), 7.90-7.82 (3H, m, Ar**H**), 7.52-7.44 (3H, m, Ar**H**), 5.87 (1H, br s, O**H**), 3.84-3.58 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.09 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.64 (3H, s, C**H**$_3$COH), 0.92 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.0 (C), 143.0 (C), 133.1 (C), 132.1 (C), 128.1 (CH), 127.7 (CH), 127.3 (CH), 125.9 (CH), 125.6 (CH), 123.9 (CH), 123.0 (CH), 74.9 (C), 66.8 (CH_2), 66.7 (CH_2), 46.3 (CH_2), 43.1 (CH), 41.9 (CH_2), 29.9 (CH_3), 13.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1749.

Data for **207d**: m.p. 105-107 °C; IR ($CHCl_3$) 3349 (OH), 2973, 2924, 2854, 1609 (C=O), 1442, 1233, 1115, 1067, 1030 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.90 (1H, s, Ar**H**), 7.83-7.79 (3H, m, Ar**H**), 7.50-7.43 (3H, m, Ar**H**), 6.00 (1H, br s, O**H**), 3.47-3.14 (7H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.96-2.86 (2H, m, CH_3C**H** and OCH_2C**H**$_2$N), 1.58 (3H, s, C**H**$_3$COH), 1.41 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.4 (C), 145.9 (C), 133.1 (C), 132.1 (C), 128.0 (CH), 127.7 (CH), 127.4 (CH), 126.1 (CH), 125.7 (CH), 123.3 (CH), 123.0 (CH), 74.9 (C), 66.4 (CH_2), 66.2 (CH_2), 46.0 (CH_2), 42.6 (CH), 41.5 (CH_2), 27.1 (CH_3), 12.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1753.

(±)-(2*R*,3*R*)-3-Furan-2-yl-3-hydroxy-2-methyl-1-morpholin-4-ylbutan-1-one (206e) and (±)-(2*R*,3*S*)-3-furan-2-yl-3-hydroxy-2-methyl-1-morpholin-4-ylbutan-1-one (207e).



206e



207e

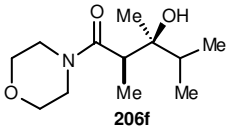
General Procedure B was followed using 2-furyl methyl ketone (121 mg, 1.10 mmol) for a reaction time of 4 h and the reaction mixture was purified by column

chromatography (20% EtOAc/petrol) to give the *aldol product* **206e** (187 mg, 72%) as a colourless oil followed by *aldol product* **207e** (54 mg, 22%) as a colourless oil.

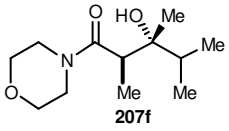
Data for **206e**: IR (film) 3388 (OH), 2976, 2932, 2858, 1617 (C=O), 1465, 1440, 1233, 1117, 1026 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35-7.34 (1H, m, C**H**), 6.38-6.37 (2H, m, 2 x C**H**), 5.40 (1H, br s, O**H**), 3.80-3.56 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.10 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.56 (3H, s, C**H**$_3$COH), 1.02 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 175.5 (C), 157.6 (C), 140.8 (CH), 110.2 (CH), 105.3 (CH), 73.4 (C), 66.8 (CH_2), 66.7 (CH_2), 46.2 (CH_2), 41.8 (CH_2), 41.2 (CH_2), 27.7 (CH_3), 13.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$: 254.1387, found: 254.1388.

Data for **207e**: IR (film) 3409 (OH), 2979, 2926, 2860, 1616 (C=O), 1469, 1445, 1232, 1115, 1031 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.29-7.28 (1H, m, Ar**H**), 6.31-6.30 (1H, m, Ar**H**), 6.24-6.23 (1H, m, Ar**H**), 5.68 (1H, br s, O**H**), 3.71-3.28 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.22 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.47 (3H, s, C**H**$_3$COH), 1.29 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.6 (C), 160.9 (C), 140.8 (CH), 110.5 (CH), 104.6 (CH), 72.5 (C), 66.7 (CH_2), 66.5 (CH_2), 46.2 (CH_2), 41.8 (CH_2), 40.5 (CH), 24.9 (CH_3), 11.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{24}NO_3$ $[M+H]^+$: 230.1751, found: 230.1749.

(±)-(2*R*,3*S*)-3-Hydroxy-2,3,4-trimethyl-1-morpholin-4-ylpentan-1-one (206f) and (±)-(2*R*,3*R*)-3-hydroxy-2,3,4-trimethyl-1-morpholin-4-ylpentan-1-one (207f).



206f



207f

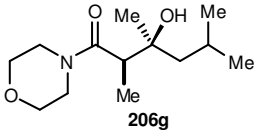
General Procedure B was followed using 3-methyl-2-butanone (118 μL, 1.10 mmol) for a reaction time of 4 h and the reaction mixture was purified by column chromatography (30% EtOAc/petrol) to give the *aldol product* **206f** (75 mg, 33%) as a pale yellow solid followed by the *aldol product* **207f** (71 mg, 31%) as a pale yellow oil. Slow evaporation of a hexane solution of **206f** provided colourless crystalline crystals that were suitable for X-ray crystallography.

Data for **206f**: m.p. 55-57 ºC; IR ($CHCl_3$) 3398 (OH), 2964, 1614 (C=O), 1465, 1371, 1266, 1231, 1117, 1031, 1011 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.31 (1H, s,

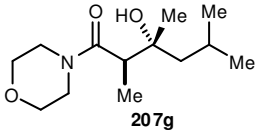
O**H**), 3.74 -3.53 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.78 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**C=O), 2.01-1.94 (1H, m, C**H**(CH$_3$)$_2$), 1.21 (3H, d, *J* = 7.1 Hz, C**H**$_3$CHC=O), 1.02 (3H, s, C**H**$_3$COH), 0.99 (3H, d, *J* = 7.0 Hz, CH(C**H**$_3$)$_2$), 0.81 (3H, d, *J* = 7.0 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 176.7 (C), 74.4 (C), 66.9 (CH$_2$), 66.7 (CH$_2$), 46.3 (CH$_2$), 41.8 (CH$_2$), 38.9 (CH), 32.9 (CH), 20.0 (CH$_3$), 17.2 (CH$_3$), 16.3 (CH$_3$), 11.4 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{12}H_{24}NO_3$ $[M+H]^+$: 230.1751, found: 230.1750.

Data for **207f**: IR (film) 3399 (OH), 2963, 1613 (C=O), 1466, 1301, 1266, 1231, 1117, 1030, 919 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 4.83 (1H, s, O**H**), 3.75-3.49 (8H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.82 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**C=O), 1.85-1.78 (1H, m, C**H**(CH$_3$)$_2$), 1.21 (3H, d, *J* = 7.1 Hz, C**H**$_3$CHC=O), 1.00 (3H, d, *J* = 5.4 Hz, CH(C**H**$_3$)$_2$) 0.98 (3H, s, C**H**$_3$COH), 0.80 (3H, d, *J* = 6.9 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz CDCl$_3$) δ 176.4 (C), 75.5 (C), 66.8 (CH$_2$), 66.7 (CH$_2$), 46.1 (CH$_2$), 41.6 (CH$_2$), 38.7 (CH), 36.1 (CH), 18.4 (CH$_3$), 17.3 (CH$_3$), 17.0 (CH$_3$), 12.7 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{12}H_{24}NO_3$ $[M+H]^+$: 230.1751, found: 230.1749.

(±)-(2*R*,3*S*)-3-Hydroxy-2,3,5-trimethyl-1-morpholin-4-ylhexan-1-one (206g) and (±)-(2*R*,3*R*)-3-hydroxy-2,3,5-trimethyl-1-morpholin-4-ylhexan-1-one (207g).



206g



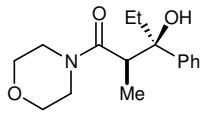
207g

General Procedure B was followed using 4-methyl-2-pentanone (138 μL, 1.10 mmol) for a reaction time of 3 h and the reaction mixture was purified by column chromatography (10% EtOAc/petrol) to give the *aldol product* **206g** (86 mg, 35%) as a colourless crystalline solid that was suitable for X-ray crystallography followed by the *aldol product* **207g** (87 mg, 36%) as a colourless oil.

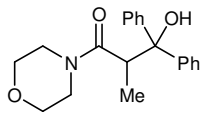
Data for **206g**: m.p. 43-45 ºC; IR (film) 3399 (OH), 2955, 2867, 1615 (C=O), 1466, 1439, 1266, 1228, 1118, 1026 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 4.49 (1H, br s, O**H**), 3.78-3.65 (6H, m, 2 x OC**H**$_2$C**H**$_2$N), 3.63-3.50 (2H, m, 2 x OC**H**$_2$C**H**$_2$N), 2.65 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**C=O), 1.87-1.77 (1H, m, C**H**(CH$_3$)$_2$), 1.53 (1H, dd, *J* = 14.1, 7.4 Hz, C**H**$_2$CH(CH$_3$)$_2$), 1.33 (1H, dd, *J* = 14.1, 4.6 Hz, C**H**$_2$CH(CH$_3$)$_2$), 1.25 (3H, s, C**H**$_3$COH), 1.21 (3H, d, *J* = 7.1 Hz, C**H**$_3$CHC=O), 1.06 (3H, d, *J* = 6.6 Hz,

$CH(CH_3)_2$), 0.98 (3H, d, *J* = 6.6 Hz, $CH(CH_3)_2$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.4 (C), 72.9 (C), 66.9 (CH_2), 66.7 (CH_2), 47.4 (CH_2), 46.3 (CH_2), 41.9 (CH), 41.7 (CH_2), 26.3 (CH_3), 25.1 (CH_3), 24.2 (CH_3), 23.9 (CH), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{26}NO_3$ $[M+H]^+$: 244.1907, found: 244.1909.

Data for **207g**: IR (film) 2409 (OH), 2953, 1615 (C=O), 1457, 1265, 1229, 1116, 1028, 848, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.36 (1H, br s, O**H**), 3.71-3.43 (8H, m, 2 x OCH_2CH_2N), 2.57 (1H, q, *J* = 7.1 Hz, $CH_3CHC{=}O$), 2.60-2.54 (1H, m, $CH(CH_3)_2$), 1.38 (1H, dd, *J* = 14.0, 7.3 Hz, $CH_2CH(CH_3)_2$), 1.27 (1H, dd, *J* = 14.0, 4.4 Hz, $CH_2CH(CH_3)_2$), 1.16 (3H, d, *J* = 7.1 Hz, $CH_3CHC{=}O$), 1.13 (3H, s, CH_3COH), 0.96 (3H, d, *J* = 6.7 Hz, $CH(CH_3)_2$), 0.87 (3H, d, *J* = 6.7 Hz, $CH(CH_3)_2$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 176.4 (C), 73.3 (C), 66.8 (CH_2), 66.6 (CH_2), 50.3 (CH_2), 46.1 (CH_2), 41.9 (CH), 41.6 (CH_2), 25.2 (CH_3), 24.2 (CH_3 and CH), 23.4 (CH_3), 12.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{26}NO_3$ $[M+H]^+$: 244.1907, found: 244.1909.



(±)-(2*R*,3*R*)-3-Hydroxy-2-methyl-1-morpholin-4-yl-3-phenylpentan-1-one (206h). The title compound was prepared according to General Procedure B from propiophenone (132 μL, 1.10 mmol) for a reaction time of 7 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (207 mg, 75%). m.p. 147-149 °C; IR ($CHCl_3$) 3349 (OH), 2970, 2932, 2857, 1612 (C=O), 1447, 1230, 1117, 1028, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.42-7.33 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 5.42 (1H, s, O**H**), 3.81-3.56 (8H, m, 2 x OCH_2CH_2N), 2.97 (1H, q, *J* = 7.1 Hz, CH_3CH), 1.90-1.71 (2H, m, CH_3CH_2C), 0.89 (3H, d, *J* = 7.1 Hz, CH_3CH), 0.67 (3H, t, *J* = 7.3 Hz, CH_3CH_2C); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.4 (C), 143.3 (C), 128.0 (2 x CH), 126.3 (CH), 125.6 (2 x CH), 77.7 (C), 66.9 (CH_2), 66.8 (CH_2), 46.4 (CH_2), 43.2 (CH), 41.9 (CH_2), 34.2 (CH_2), 13.0 (CH_3), 7.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1754.

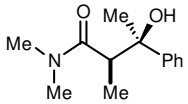


3-Hydroxy-2-methyl-1-morpholin-4-yl-3,3-diphenylpropan-1-one (206i). The title compound was prepared according to General Procedure B from benzophenone (200 mg, 1.10 mmol) for a

reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (202 mg, 62%). m.p. 108-110 °C; IR ($CHCl_3$) 3324 (OH), 2971, 2922, 2856, 1613 (C=O), 1448, 1230, 1116, 1032, 751 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.46 (4H, m, Ar**H**), 7.33-7.26 (4H, m, Ar**H**), 7.21-7.15 (2H, m, Ar**H**), 6.43 (1H, s, O**H**), 3.78 (1H, q, *J* = 7.0 Hz, $CH_3C\mathbf{H}$), 3.73-3.42 (8H, m, 2 x $OC\mathbf{H}_2C\mathbf{H}_2N$), 1.17 (1H, d, *J* = 7.0 Hz, $C\mathbf{H}_3CH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.7 (C), 148.0 (C), 144.6 (C), 128.2 (2 x CH), 128.1 (2 x CH), 126.7 (CH), 126.5 (CH), 125.5 (2 x CH), 125.2 (2 x CH), 78.6 (C), 66.7 (CH_2), 66.5 (CH_2), 46.1 (CH_2), 41.7 (CH_2), 41.4 (CH), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found: 326.1752.

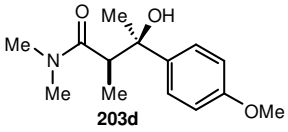
Stereochemical Determinations

The relative stereochemistry of the known aldol product **203a** was assigned by comparison with literature spectral data.[57]

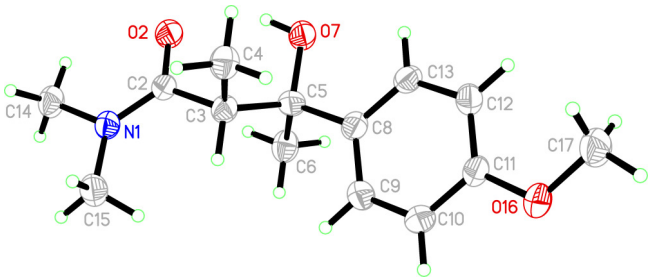


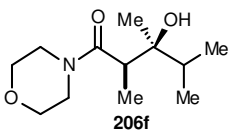
203a

The relative stereochemistries of **203d**, **206f** and **206g** were determined by X-ray crystallography.

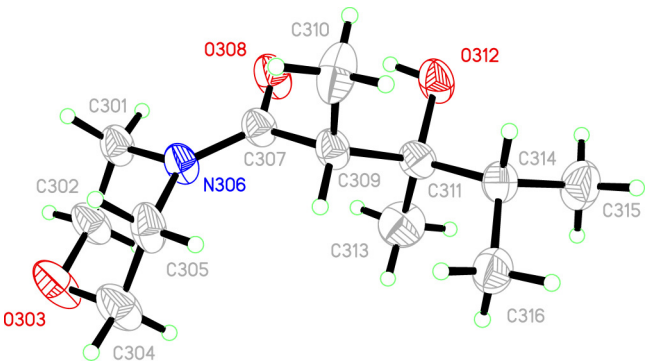


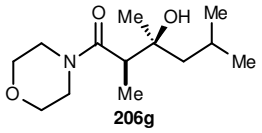
203d



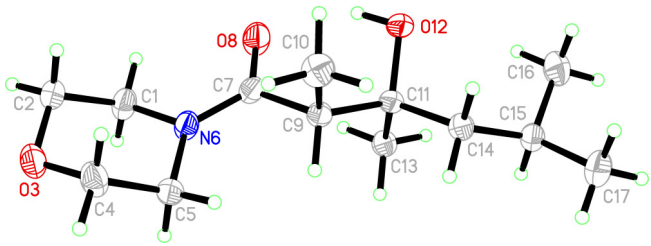


206f





206g



The relative stereochemistries of the remaining products **203a-k** and **206a-i** were assigned by analogy.

2.5 References

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3 Asymmetric Cobalt-Catalysed Reductive Aldol Reactions[i]

3.1 Introduction

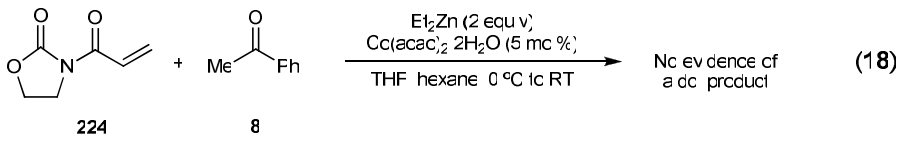
Having demonstrated the utility of the cobalt-catalysed intermolecular reductive aldol reaction, the development of an asymmetric variant was now sought. The development of a stereocontrolled reductive aldol reaction with a ketone electrophile is a valuable endeavour, as it allows access to chiral tertiary alcohols, structural units present in numerous biologically active molecules. Compared with aldehydes however, there are relatively few effective methods for controlling the absolute stereochemical outcome of ketone aldol reactions. There are three main reasons for this paucity: 1) ketones are less reactive than aldehydes; 2) problems with retroaldolisation; 3) smaller differences in the steric properties between the two substituents on the ketone carbonyl, which is usually manifested in low levels of diastereoselection and enantiofacial selectivity.

3.2 Results and Discussion

Initially, the development of an asymmetric variant was pursued by the utilisation of chiral cobalt-ligand complexes. According to the proposed mechanistic hypothesis (Scheme 24, chapter 2), cobalt is not a participant in the aldol reaction and therefore no enantioselection would be expected. Trials with suitable sub-stoichiometric quantities of various chiral ligands support this hypothesis as no enantioselection in any of the reactions was observed.

As a result of these observations, attention was turned to a chiral auxiliary strategy. Auxiliary candidates were sought that would impart high levels of diastereofacial selectivity, as well as deliver high reaction efficiencies. An excellent first choice for screening seemed to be the *N*-alkenoyloxazolidinone **224** (Eq 18).[67]

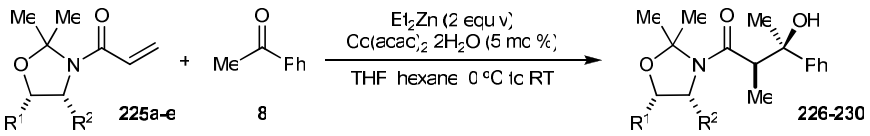
[i] The work in this chapter was done in collaboration with Pekka M. Joensuu

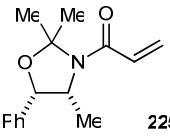
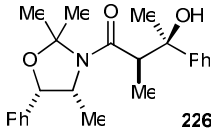
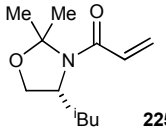
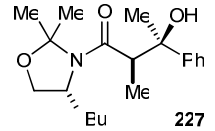
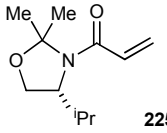
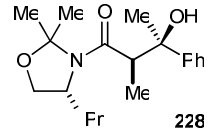
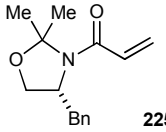
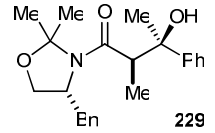
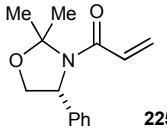
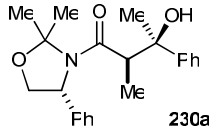


(18)

However under our reaction conditions, no aldol products were observed. Since *N*-alkenoyloxazolidinones had failed to yield the desired aldol product, a selection of *N*-acryloyloxazolidines derived from different amino acids were screened for selectivity and efficiency (Table 30).[68]

Table 30: Screening of Different Oxazolidines Auxiliaries[a]



Entry	Oxazolidine Auxiliary	Product[b]	dr[c]
1	 225a	 226	2:1
2	 225b	 227	3:1
3	 225c	 228	5:1
4	 225d	 229	5:1
5	 225e	 230a	11:1

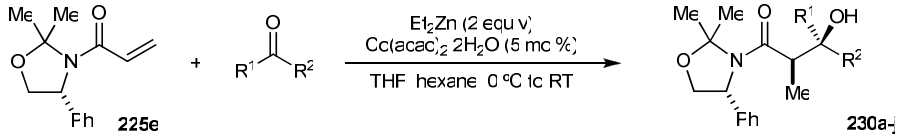
a) Reactions were conducted using 1.0 mmol of the oxazolidine auxiliary and 1.1 mmol of acetophenone in THF (5 mL) and hexane (2 mL) for 24 h. b) The major *cis* isomer is shown c) dr = (major isomer):Σ(other isomers). Determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixtures

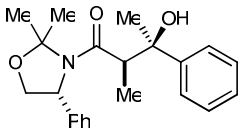
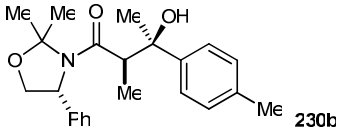
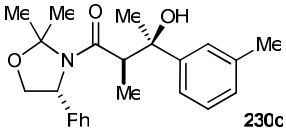
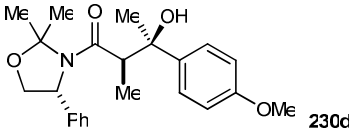
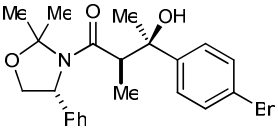
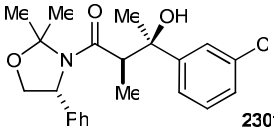
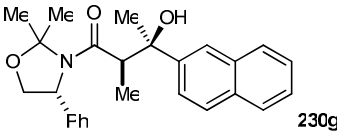
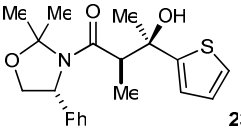
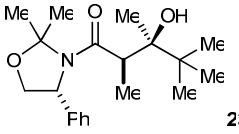
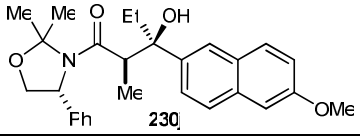
Initially, the result of the reaction of oxazolidine **225a** (entry 1) was encouraging since although the diastereoselectivity was a low 2:1 [major isomer/Σ(other isomers)], smooth conversion to product was obtained. The low selectivity was

attributed to the relatively small size of the methyl group in the R^2 position. In an attempt to improve the diastereoselectivity, several more auxiliaries were tested with larger groups in the R^2 position. Although the use of isobutyl, isopropyl, and benzyl groups (entries 2-4) did result in improved selectivity, a number of unidentified side products were also obtained. These results were still encouraging however, as they clearly demonstrated that the steric influence of R^2 was the controlling factor in improving diastereoselectivity. Fortunately, the use of a phenyl group at the R^2 position resulted in clean conversion to the desired aldol product **230** with a diastereoselectivity of 11:1 (entry 5).

With an effective chiral auxiliary now in hand, the scope of the reaction with respect to varying the ketone reactant was now explored (Table 31).

Table 31: Cobalt-Catalysed Reductive Aldol Reactions of *N*-Acryloyloxazolidine 225e with Ketones[a]



Entry	R^1	R^2	Product	dr[b,c]	Yield(%)[d]
1	Me	Ph	 230a	11:1	73
2	Me	4-MePh	 230b	9:1	76
3	Me	3-MePh	 230c	12:1	72
4	Me	4-MeOPh	 230d	8.5:1	72
5	Me	4-BrPh	 230e	12:1	63
6	Me	3-ClPh	 230f	7:1	58
7	Me	2-Naphthyl	 230g	13:1	75
8	Me	2-thienyl	 230h	6:1	61
9	Me	*t*-Bu	 230i	n/a	0[e]
10	Et	6'-MeO-2-Naphthyl	 230j	6:1	59

a) Reactions were conducted using 1.0 mmol of **225e** and 1.1 mmol of ketone in THF (5 mL) and hexane (2 mL) for 3–17 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) dr = (major isomer):Σ(other isomers). d) Isolated yield of major diastereomer. e) A complex mixture was obtained.

Acetophenone and acetophenone derivatives of varying electronic properties are tolerated affording aldol products in up to 76% yield and with diastereoselectivities of up to 12:1 (entries 1-6). Acryloyloxazolidine (**225e**) also underwent reaction with ketones bearing naphthyl (entries 7 and 10), heteroaromatic (entry 8), and napthyl substituents (entry 10). Aliphatic ketones proved to be less suitable substrates in this reaction, providing a complex mixture of products (entry 9). The relative stereochemistries of **230a**, and **230d** were determined by X-ray crystallography (Figure 7). The relative stereochemistry of the remaining aldol products was assigned by analogy.

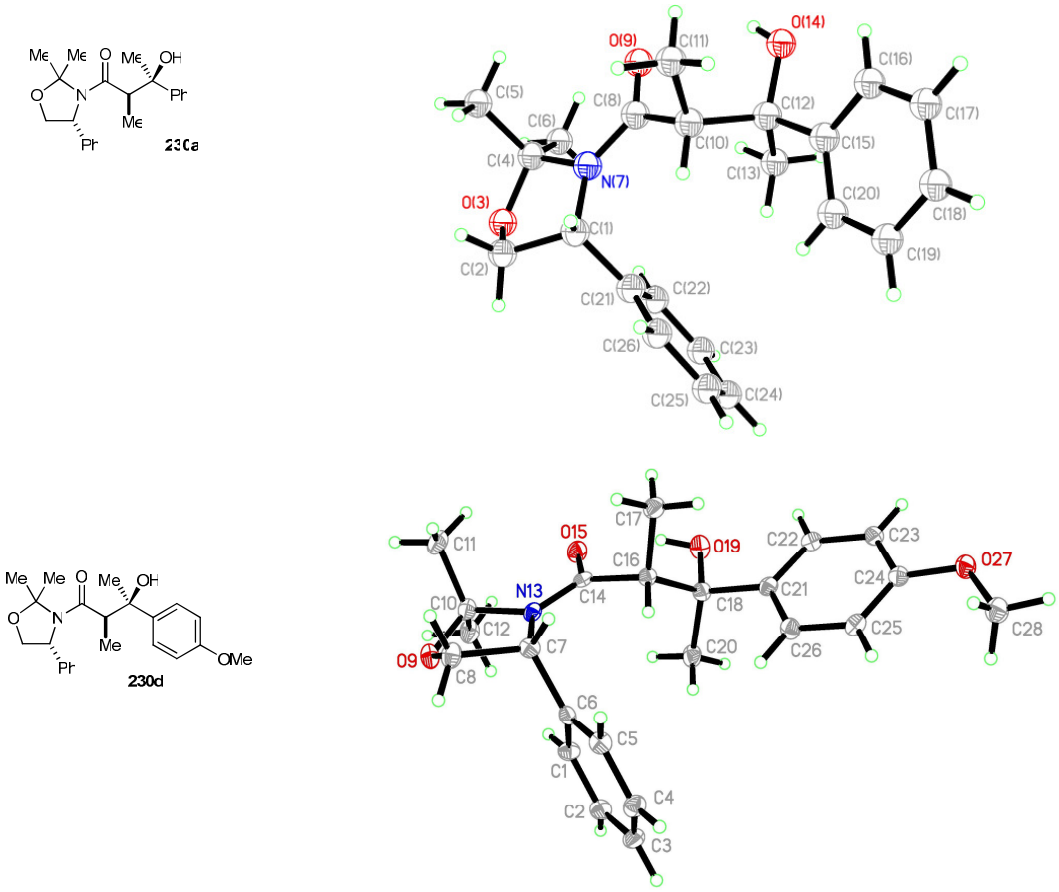
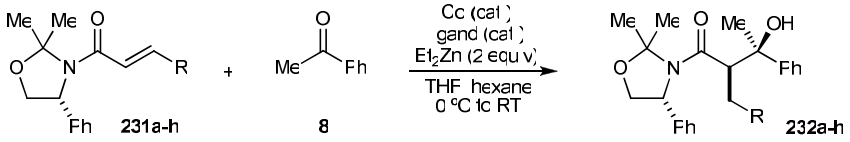


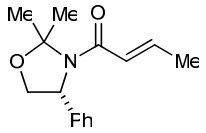
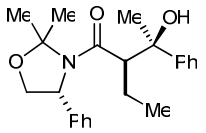
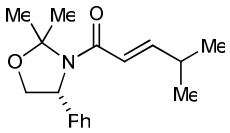
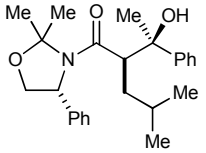
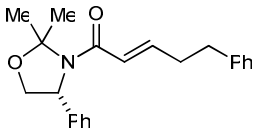
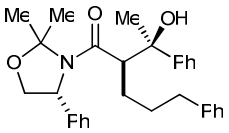
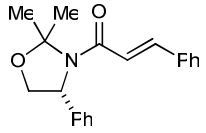
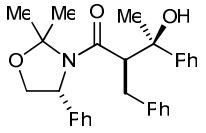
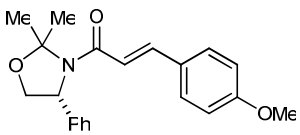
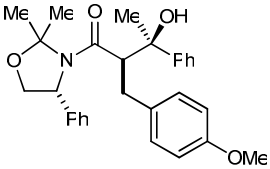
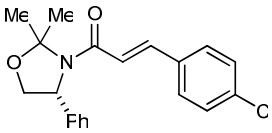
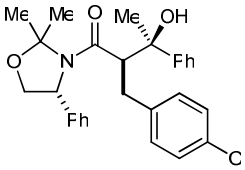
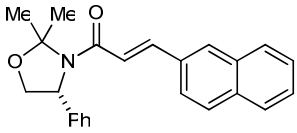
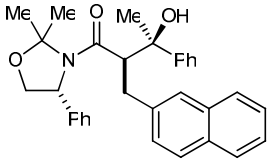
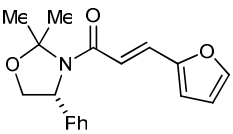
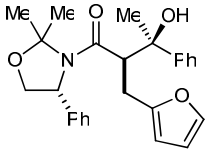
Figure 7: X-ray Crystal Structures of Aldol Products 230a and 230d

Having established the scope of reactions with *N*-acryloyloxazolidines, attention was turned to examining the effect of substitution at the β-carbon of the double bond. A range of substituted *N*-alkenoyloxazolidines (**231a-h**) were reacted with acetophenone (**8**) (Table 32). These reactions were performed by Pekka M. Joensuu.

Table 32[i]: Reactions of Substituted *N*-Alkenoyloxazolidines with Acetophenone[a]



Method A: $Cc(acac)_2 \cdot 2H_2O$ (5 mol %)
Method B: $CcCl_2$ (5 mol %), Cy_2PFh (5.5 mol %)

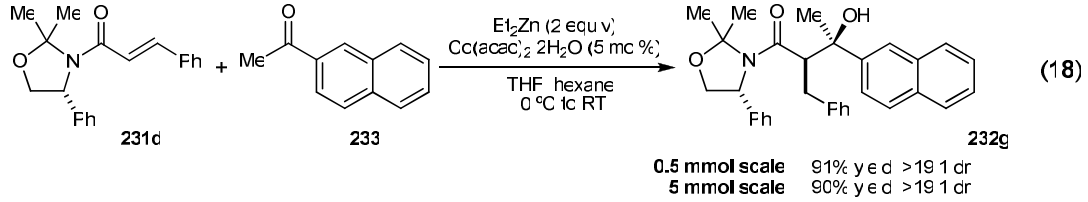
Entry/ Method	Substrate		Product		dr[b,c]	Yield (%)[d]
1/B		**231a**		**232a**	16:1	82
2/B		**231b**		**232b**	15:1	79
3/B		**231c**		**232c**	15:1	80
4/A		**231d**		**232d**	>19:1	86
5/A		**231e**		**232e**	>19:1	86
6/A		**231f**		**232f**	>19:1	84
7/A		**231g**		**232g**	>19:1	90
8/A		**231h**		**232h**	>19:1	83

a) Reactions were conducted using 0.5 mmol of **231a-h** and 0.55 mmol of acetophenone in THF (2.5 mL) and hexane (1 mL) for 4–6 h. b) Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. c) dr = (major isomer):Σ(other isomers). d) Isolated yield of major diastereomer.

[i] Reactions performed by Pekka M. Joensuu.

As was the case in the earlier racemic reactions (see chapter 2), substitution at the β-carbon of the double bond greatly increases diastereoselectivity (≥15:1). In addition, the reactions of **231a-h** were cleaner, with less side reactions than those of *N*-acryloyloxazolidine **225e**, resulting in higher isolated yields of products. Incomplete conversions were observed with alkyl-substituted acrylamides **231a-c** using $Co(acac)_2 \cdot 2H_2O$ as the pre-catalyst. In earlier work (see Table 23, page 46) a combination of $CoCl_2$ and Cy_2PPh had been effective in driving the reactions to completion. This combination was used again with much improved results (entries 1–3). Aromatic and heteroaromatic-substituted *N*-alkenoyloxazolidines were the best substrates in these reactions, affording aldol products in 83–90% yield as one observable diastereomer (>19:1 by ^1H NMR analysis) (entries 4-8).

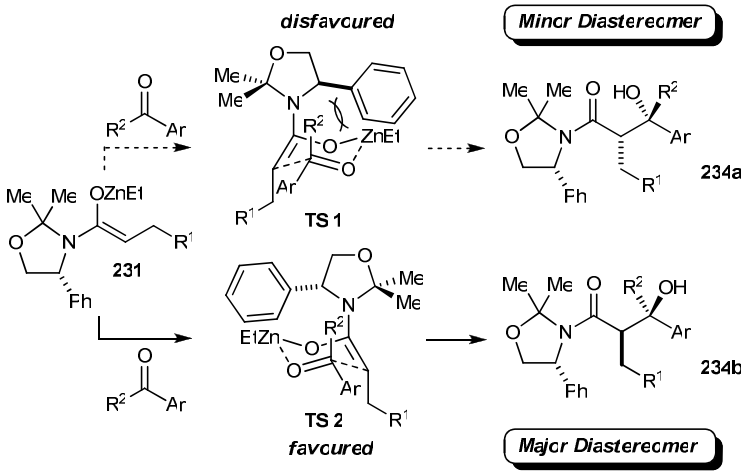
The yields and diastereoselectivities of these reactions are maintained on increasing the scale. For example, reaction of cinnamoyl-substituted oxazolidine **231d** with 2-acetonaphthone provided **232g** in comparable yield whether performed on a 0.5 mmol or 5 mmol scale (Eq 18)[i].



(18)

The observed asymmetric induction in these reactions is consistent with the intervention of *Z*-zinc enolates **231** and chelated chair-like Zimmerman–Traxler transition states[69] in which the geminal dimethyl groups of the oxazolidine are orientated anti to the enolate oxygen to minimise unfavourable non-bonding interactions. Inspection of alternative transition states **TS 1** and **TS 2** reveals that the oxazolidine phenyl substituent suffers fewer nonbonding interactions in **TS 2**, which leads to the observed stereochemistry of the major isomer **234b** (Scheme 26).

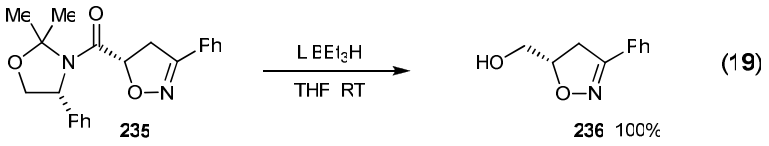
[i] Reactions performed by Pekka M. Joensuu.



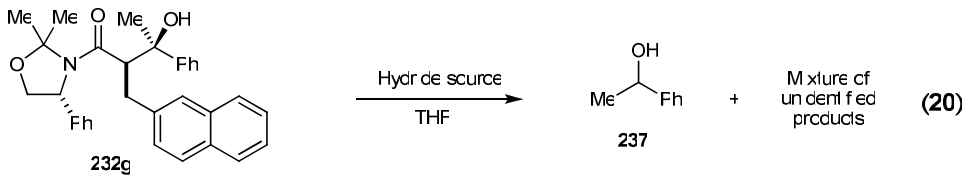
Scheme 26: Model for Stereochemical Outcome

3.3 Efforts Towards the Removal of the Chiral Auxiliary

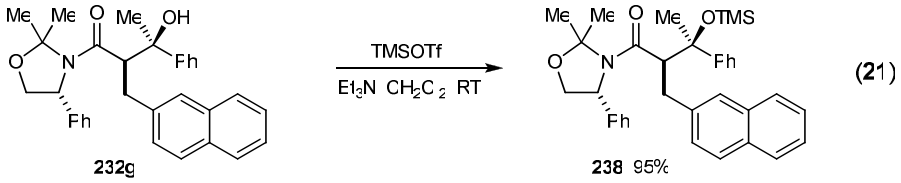
The utility of this methodology is only fully apparent when it includes the cleavage of the oxazolidine auxiliary from the aldol products in high yield. On the basis of literature precedent it was expected that this would be a straightforward task. Kanemasa and Onimura removed the same auxiliary using $LiBEt_3H$ to reduce **235** at room temperature and in quantative yield (Eq 19).[70]



Since Kanemasa and Onimura had achieved the removal of the auxiliary by reductive cleavage, initial attempts to remove the oxazolidine of **232g** were made using various hydride reagents including $LiBEt_3H$, $NaBH_4$, $LiAlH_4$, DIBAL, and lithium amidotrihydroborate (LiH_2NBH_3, "LAB").[71] However, it quickly became apparent that at low to moderate temperatures there was no reaction, while at elevated temperatures, only retroaldol fragmentation was observed to give **237** (Eq 20).

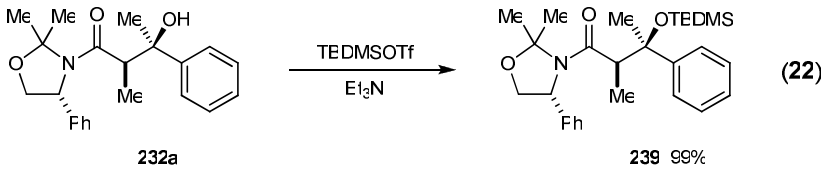


In an effort to prevent the problem of retroaldol fragmentation, **232g** was protected as a TMS ether (Eq 21).



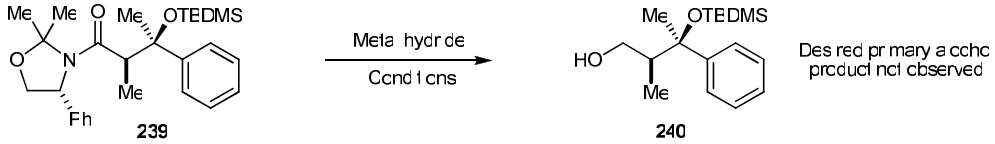
The TMS protected **238** was now subjected to the same hydride reduction conditions as the un-protected **232g**. Unfortunately, no reaction was observed at low to medium temperatures, and at elevated temperatures, there was either no reaction or more usually, the protecting group was removed in which case retroaldol fragmentation followed.

It was proposed there were two problems; i) the TMS protecting group was being removed at higher temperatures 2) the steric bulk of **232g** may be what was hindering attack by the hydride anion during a reductive cleavage reaction. In an effort to remedy both these problems, the smaller, less sterically congested aldol product **232a** was protected as a TBDMS ether (Eq 22).



The silyl ether **239** was now subjected to a range of reductive cleavage reactions (Table 33).

Table 33: Attempted Removal of the Chiral Auxiliary from Silyl Ether 239 with Metal Hydrides



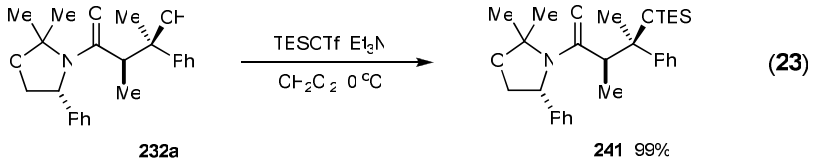
Entry	Metal Hydride	Solvent, Temperature	Observations
1	$Li(CH_2)_4NBH_3$	THF, 0 °C to reflux	No reaction
2	$LiAlH_4$	THF, 0 °C to RT	No reaction
3	$LiAlH_4$	THF, reflux	Mixture of products, **237**[a] observed, protecting group removed
4	LiH_2NBH_3	THF, 0 °C to RT	No reaction
5	LiH_2NBH_3	THF, reflux	Protecting group removed only
6	LiH_2NBH_3	dioxane, reflux	No reaction
7	$LiBHEt_3$	THF, 0 °C	No reaction
8	$LiBHEt_3$	THF, RT	Low conversion, unidentified products
9	$LiBHEt_3$	THF, reflux	Mixture of products, **237**[a] observed, protecting group removed

a) Determined by ^1H NMR analysis of the unpurified reaction mixture

At low to moderate temperatures, generally no reaction was observed at all, although in the case of the reaction with $LiBHEt_3$ (entry 8) low conversion to a mixture of unidentified products was observed. At higher temperatures, there was either no reaction (entries 1, and 6), or a complex mixture of products was observed, usually combined with the removal of the TBDMS group (as in entries 3 and 9). In one example (entry 5), the protecting group was removed leaving the starting material intact.

The TMS protecting group had proved to be unstable at elevated temperatures while the TBDMS protecting group was possibly too sterically bulky to allow attack by the hydride anion during a reductive cleavage reaction. A TES protecting group was then selected as a possible compromise between stability and size that would hopefully be

stable under reductive cleavage conditions but not so large that it would hinder the reaction. Oxazolidine **232a** was therefore protected as a TES ether (Eq 23).

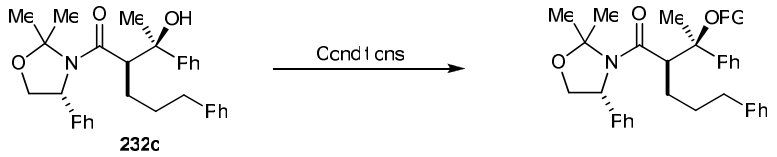


232a **241** 99% (**23**)

In the event, although the silyl ether **241** was stable, even under reflux conditions, there was no reductive cleavage observed.

Since attempts to remove the oxazolidine auxiliary had failed with silyl protecting groups, attention was turned to protecting the tertiary alcohol with more stable groups including benzyl (Bn-), methylethylmethyl (MEM-), and acetyl (Ac-) (Table 34).

Table 34: Attempted Protection of Tertiary Alcohol with Bn-, MEM-, and Ac- Protecting Groups[i]



232c

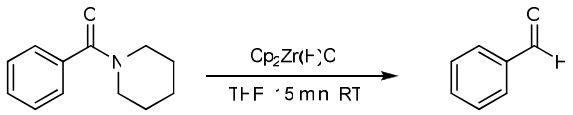
Entry	PG[a]	Conditions	Observations
1	Bn	BnBr, NaH, THF, 0 °C to RT	Mixture of unidentified products
2	Bn	BnBr, Bu_4Ni, NaH, 0 °C to RT	Mixture of unidentified products
3	Bn	benzyl-trichloroacetimidate, CF_3SO_3H, CH_2Cl_2, 0 °C	Starting material recovered
4	Bn	benzyl-trichloroacetimidate, CF_3SO_3H, CH_2Cl_2, 0 °C to RT	Mixture of unidentified products
5	Bn	benzyl-trichloroacetimidate, CSA, CH_2Cl_2, 0 °C to RT	Starting material recovered
6	MEM	MEMCl, *i*-Pr_2NEt, CH_2Cl_2, RT	Starting material recovered
7	MEM	MEMCl, *i*-Pr_2NEt, DCE, reflux	Starting material recovered
8	MEM	MEMCl, *i*-Pr_2NEt, Bu_4NI, DCE, reflux	Starting material recovered
9	Ac	Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C	Starting material recovered
10	Ac	Ac_2O (as solvent), DMAP, Et_3N, 0 °C	Starting material recovered

a) PG = protecting group

As can be seen from Table 34, all attempts to protect the tertiary alcohol with Bn-, MEM-, or Ac- did not succeed. The difficulty in introducing these protecting groups is likely caused by the extreme steric hindrance surrounding the tertiary alcohol coupled with the propensity of the said hydroxyl group to eliminate under more vigorous conditions.

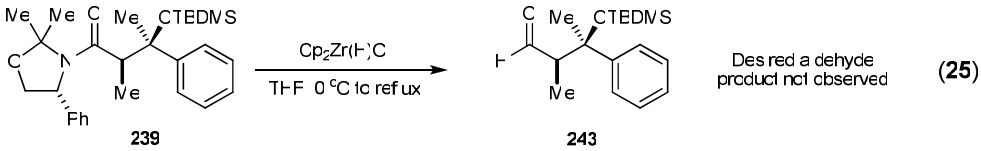
[i] Reactions performed by Pekka M. Joensuu.

Georg and co-workers reported a very mild procedure where by $Cp_2Zr(H)Cl$ (Schwartz reagent) is used to mediate the reduction of amides to aldehydes under mild conditions at room temperature (Eq 24).[72]



242 2 84% (24)

In order to test these reaction conditions on the oxazolidine auxiliary, reactions were performed using silyl ether **239** (Eq 25).

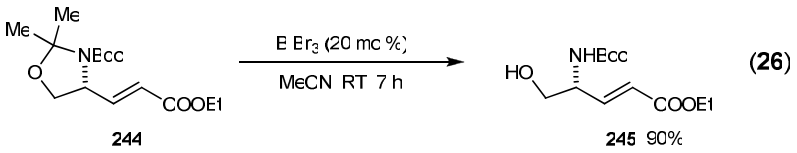


239 243 (25)

Reaction performed at lower temperatures resulted only in the recovery of the starting sily ether **239**. Raising the temperature to reflux caused removal of the sily ether protecting group, the rest of the molecule remained intact. The desired aldehyde product **243** was not detected.

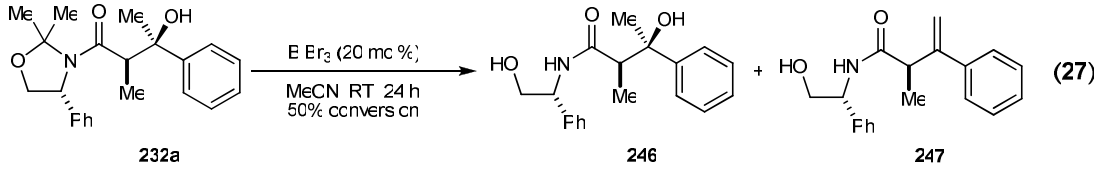
Having been unsuccessful in removing the auxiliary by means of reductive hydride cleavage, attention was turned to an acid- or base-catalysed removal strategy. Using aldol product **232a**, initial efforts focused on the use of NaOH in t-BuOH, MeOH and H_2O. The reaction was refluxed for 24 hours but only the starting substrate was observed. Two more reactions were performed using either $La(OTf)_3$ or $Yb(OTf)_3$ in MeOH and MeCN but in these reactions, only unreacted starting material was recovered. The same result was obtained when PTSA in MeOH and water was refluxed for 24 hours. Using stronger acids like H_2SO_4 in dioxane or F_3CCOOH in THF resulted in decomposition, whereas the use of weaker acids like TFA and acetic acid resulted in only the recovery of starting material.

Another strategy was to remove the auxiliary in a stepwise fashion. Yao and co-workers reported conditions for removing the geminal dimethyl group from N-acyl oxazolidines with the use of $BiBr_3$ (Eq 26).[73]



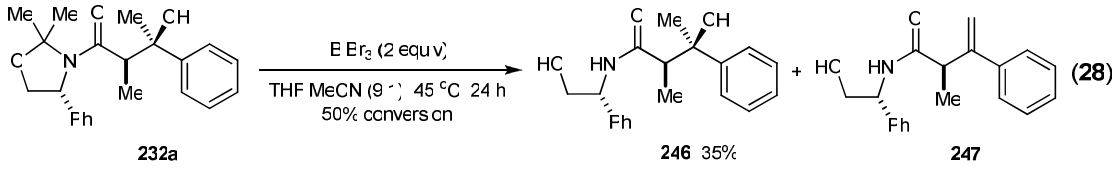
(26)

These conditions were applied to oxazolidine aldol product **232a** (Eq 27).



(27)

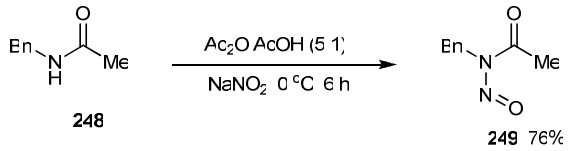
From analysis of the unpurified reaction mixture, it was apparent that only around 50% of **232a** had reacted. The 50% that had reacted had been converted into two products. One was the desired secondary amine **246** and the other was an undesired side product **247**, created from the elimination of the tertiary alcohol from **246**. Clearly, if the reaction was to become viable, its efficiency must be drastically improved. After exhaustive screening, the optimal reaction conditions are presented in Eq 28.



(28)

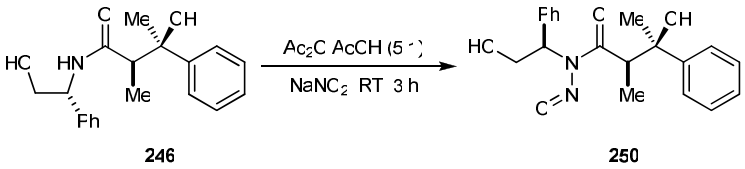
Unfortunately, 50% conversion was the best that could be obtained although the ratio of desired product to undesired product was improved from 1:1 to 5:1 in favour of the desired product. Although these conditions were far from ideal, the final two steps to remove the remainder of the auxiliary were attempted. The cleavage of the secondary amide was to be achieved first by functionalising the nitrogen with a nitroso group to make the auxiliary a better leaving group.

Wille and co-workers reported conditions for the addition of a nitroso group to a secondary amine (Eq 29).[74]



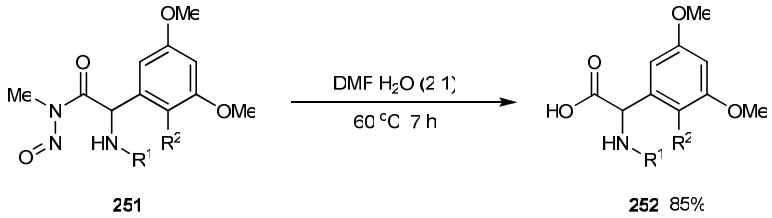
(29)

These conditions were applied to the secondary amine **246** (Eq 30).



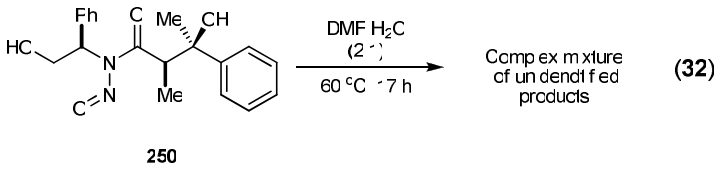
(30)

From ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture, it was not possible to determine whether the reaction had been successful. Thin layer chromatographic analysis did indicate that **246** had been consumed in the reaction. Purification of the unpurified reaction mixture was ruled out on the grounds that the nitroso group was likely too unstable. It was decided to proceed to the second step of the auxiliary removal despite the uncertain result of the first step. Evans and co-workers achieved the hydrolysis of the *N*-nitroso amide **251** by heating in a solution of DMF and water (Eq 31).[75]



(31)

These conditions were applied to the mixture that resulted from the reaction in Eq 30, based on the assumption that **250** had been formed (Eq 32).



250

(32)

Unfortunately, no trace of product was observed and only a complex mixture of unidentified products was obtained. The sub-optimal yield from the $BiBr_3$ step, coupled with the failure of the steps presented in Eqs 30 and 32 meant work in this area was discontinued.

3.4 Conclusions

Building on the work of chapter 2, an asymmetric reaction was developed using an oxazolidine chiral auxiliary. A current disadvantage of the reaction is the stability of the chiral auxiliary which has meant all efforts to remove the auxiliary have been frustrated. Two key properties are likely responsible for the oxazolidine auxiliaries stability. One is the low reactivity exhibited by the amide carbonyl, presumably due to high steric shielding caused by multiple groups around the amide. The second is the presence of the tertiary alcohol which is prone to elimination, which results in the destruction of one or both of the stereocentres. It is hoped this study has defined structural features for an auxiliary that impart high levels of asymmetric induction and that this information may provide useful information for the design of improved auxiliaries in the future.

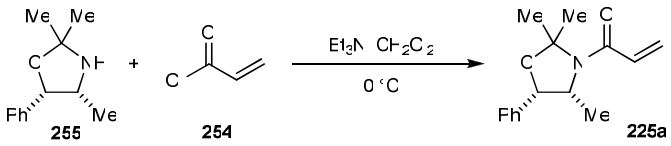
3.5 Experimental

3-Acryloyl-oxazolidin-2-one (224).

253 254 224

To a solution of oxazolidinone **253** (871 mg, 10 mmol) in THF (20 mL) at -78 °C was added BuLi (1.44 M solution in THF, 6.95 mL, 10 mmol) dropwise over 15 min. The reaction was stirred at -78 °C for 15 min then acryloyl chloride (**254)** (1.28 mL, 15.5 mmol) in THF (5 mL) was cannulated into the reaction mixture maintaining the temperature at -78 ^{o}C after which the reaction was stirred for 30 mins at -78 ^{o}C and for 15 mins at 0 ^{o}C. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) afforded oxazolidinone **224** (214 mg, 84%) as a white solid. m.p. 151 - 153 °C; IR ($CHCl_3$) 3103, 3030, 1774 (C=O), 1678 (C=O), 1622, 1354, 1223, 1113, 1039, 762 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.88-7.86 (2H, m, C**H**=C**H**), 7.63-7.58 (2H, m, Ar**H**), 7.42-7.37 (3H, m, Ar**H**), 4.47-4.41 (2H, m, OC**H**$_2$CH$_2$N), 4.14-4.08 (2H, m, OCH$_2$C**H**$_2$N); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 165.3 (C), 153.5 (C), 146.1 (CH), 134.4 (C), 130.6 (CH), 128.8 (2 x CH), 128.5 (2 x CH), 116.5 (CH), 62.0 (CH_2), 42.7 (CH_2). These spectral data are consistent with those reported previously.[76]

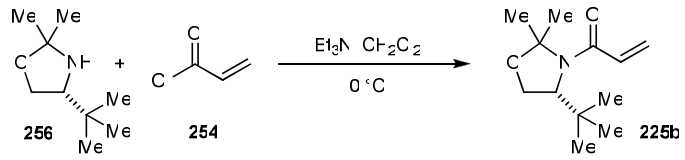
1-((4R,5*S*)-2,2,4-Trimethyl-5-phenyl-oxazolidin-3-yl)-propenone (225a).



255 254 225a

To a solution of methyl-phenyl substituted oxazolidine **255** (821 mg, 4.30 mmol), and Et_3N (719 μL, 5.16 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise acryloyl chloride (**254**) (282 μL, 3.47 mmol) over 15 min. The reaction was stirred at 0 °C for 30 min, quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) afforded *N*-alkenoyloxazolidine **225a** (843 mg, 80%) as a white solid. m.p. 257 - 259 °C; $[\alpha]_D^{21}$ –108.7 (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 2981, 2937, 1641 (C=O), 1423, 1373, 1242, 1184, 1001, 912, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.63-7.25 (5H, m, Ar**H**), 6.47-6.45 (2H, m, CH=C**H**$_2$), 5.71 (1H, dd, *J* = 7.2, 5.0 Hz, C**H**=CH$_2$), 5.30 (1H, d, 5.2 Hz, C**H**CHCH$_3$), 4.27 (1H, dq, *J* = 6.6, 5.2 Hz, CHC**H**CH$_3$), 1.84 (3H, s, C**H**$_3$), 1.74 (3H, s, C**H**$_3$), 0.88 (3H, d, *J* = 6.6 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 162.1 (C), 136.0 (C), 129.1 (CH), 128.3 (2 x CH), 128.2 (CH_2), 127.9 (CH), 126.1 (2 x CH), 94.7 (C), 78.1 (CH), 56.8 (CH), 27.1 (CH_3), 23.7 (CH_3), 17.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1489, found: 246.1493.

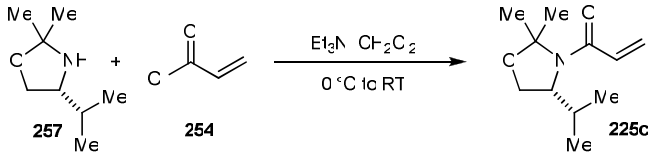
1-((*R*)-4-*tert*-Butyl-2,2-dimethyl-oxazolidin-3-yl)-propenone (225b).



To a solution of t-butyl substituted oxazolidine **256** (211 mg, 1.34 mmol), Et_3N (225 μL, 1.61 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise acryloyl chloride (**254**) (131 μL, 1.61 mmol) over 15 min. The reaction was stirred at 0 °C for a further 15 min and then quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded *N*-alkenoyloxazolidine **225b** (140 mg, 49%) as a white solid. m.p. 56 - 58 °C; $[\alpha]_D^{21}$ –92.0 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2962,

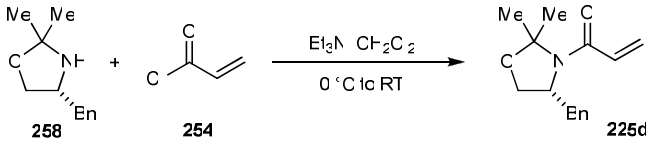
2873, 1649 (C=O), 1616, 1415, 1360, 1227, 1076, 982, 839 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.53 (1H, dd, *J* = 16.6, 9.8 Hz, C**H**=CHH), 6.35 (1H, dd, *J* = 16.6, 2.1 Hz, CH=CH**H**), 5.70-5.61 (1H, m, CH=C**H**H), 4.06-4.02 (1H, m, OC**H**$_2$CH), 3.97-3.91 (1H, m, OC**H**$_2$CH), 3.83-3.77 (1H, m, OCH$_2$C**H**), 1.76 (3H, s, C**H**$_3$), 1.54 (3H, s, C**H**$_3$), 0.95 (9H, s, (C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 164.9 (C), 130.6 (CH), 129.4 (C), 127.2 (CH_2), 65.0 (CH_2), 64.9 (CH), 35.7 (C), 27.6 (3 x CH_3), 26.3 (CH_3), 22.9 (CH_3); These spectral data are consistent with those reported previously.[77]

1-((*R*)-4-Isopropyl-2,2-dimethyl-oxazolidin-3-yl)-propenone (225c).



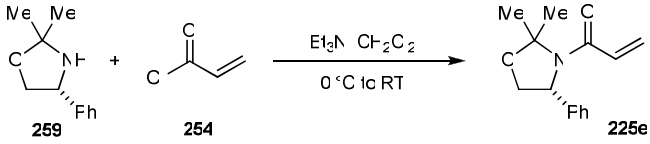
To a solution of *i*-propyl substituted oxazolidine **257** (231 mg, 1.62 mmol), Et_3N (270 μL, 1.94 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise acryloyl chloride (**254)** (157 μL, 1.94 mmol) over 15 min. The reaction was stirred at 0 °C for 30 min and then at room temperature for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) afforded *N*-alkenoyloxazolidine **225c** (96 mg, 30%) as a colourless oil. $[\alpha]_D^{21}$ –57.7 (*c* 1.00, $CHCl_3$); IR (film) 2963, 2944, 1635 (C=O), 1420, 1381, 1233, 1114, 1029, 911, 723 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.41-6.38 (2H, m, CH=C**H**$_2$), 5.66 (1H, dd, *J* = 7.2, 5.0 Hz, C**H**=CH$_2$), 3.97-3.70 (3H, m, OC**H**$_2$C**H**N), 2.07-1.91 (1H, m, CH$_3$C**H**CH$_3$), 1.70 (3H, s, C**H**$_3$), 1.54 (3H, s, C**H**$_3$), 0.95-1.54 (6H, m, C**H**$_3$CHC**H**$_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 163.0 (C), 129.6 (CH), 127.8 (CH_2), 95.5 (C), 64.3 (CH_2), 62.1 (CH), 31.9 (CH), 25.8 (CH_3), 22.9 (CH_3), 19.7 (CH_3), 17.1 (CH_3); These spectral data are consistent with those reported previously.[76]

1-((*R*)-4-Benzyl-2,2-dimethyl-oxazolidin-3-yl)-propenone (225d).



To a solution of benzyl substituted oxazolidine **258** (600 mg, 3.16 mmol), and Et_3N (528 μL, 3.79 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise acryloyl chloride (**254**) (282 μL, 3.47 mmol) over 15 mins. The reaction was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) afforded the *N*-alkenoyloxazolidine **225d** (469 mg, 61%) as a yellow oil; $[\alpha]_D^{21}$ –166.6 (*c* 1.02, $CHCl_3$); IR (film) 2983, 1651 (C=O), 1614, 1421, 1371, 1294, 1244, 978, 847, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.19 (5H, m, Ar**H**), 6.50 (1H, dd, *J* = 16.6, 9.2 Hz, C**H**CHH), 6.40 (1H, dd, *J* = 16.6, 3.0 Hz, CHC**H**H), 5.70 (1H, dd, 9.2, 3.0 Hz, CHCH**H**), 4.18-4.10 (1H, m, OCH**H**CHCH$_2$Ph), 3.89 (2H, s, CHHCHC**H$_2$**Ph), 2.99 (1H, dd, *J* = 13.6, 4.4 Hz, OC**H**HCHCH$_2$Ph), 2.88 (1H, dd, *J* = 13.6, 10.1 Hz, OCHHC**H**CH$_2$Ph), 1.77 (3H, s, C**H$_3$**), 1.59 (3H, s, C**H$_3$**); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 162.2 (C), 137.2 (C), 129.2 (2 x CH), 128.9 (CH), 128.9 (2 x CH), 128.1 (CH_2), 126.9 (CH), 95.7 (C), 66.4 (CH_2), 59.0 (CH), 40.9 (CH_2), 26.7 (CH_3), 23.1 (CH_3).). These spectral data are consistent with those reported previously.[76]

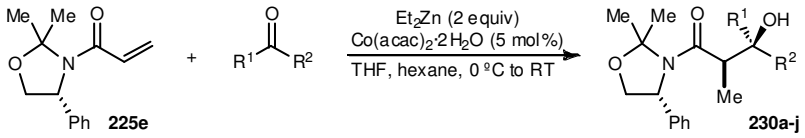
1-((*R*)-2,2-Dimethyl-4-phenyl-oxazolidin-3-yl)-propenone (225e).



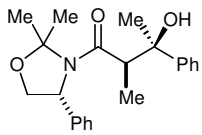
To a solution of phenyl substituted oxazolidine **259** (3.00 g, 16.95 mmol), and Et_3N (2.84 mL, 20.34 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise acryloyl chloride (**254)** (7.32 mL, 86.94 mmol) over 15 min. The reaction was stirred at 0 °C

for 30 min and then at room temperature for 20 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) afforded the *N*-alkenoyloxazolidine **225e** (1.67 g, 43%) as a yellow solid. m.p. 47 - 49 °C; $[\alpha]_D^{21}$ –87.8 (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 2985, 1653 (C=O) 1612, 1421, 1363, 1252, 1061, 976, 843, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.27 (5H, m, Ar**H**), 6.31 (1H, dd, *J* = 16.6, 2.1 Hz, CHCH**H**), 6.11 (1H, dd, *J* = 16.6, 10.1 Hz, CHC**H**H), 5.47 (1H, dd, 10.1, 2.1 Hz, C**H**CHH), 5.03 (1H, dd, *J* = 6.5, 2.3 Hz, OC**H**HCHPh), 4.40 (1H, dd, *J* = 8.9, 6.5 Hz, OCHHC**H**Ph), 3.94 (1H, dd, *J* = 8.9, 2.3 Hz, OCH**H**CHPh), 1.91 (3H, s, C**H**$_3$), 1.71 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 163.3 (C), 141.4 (C), 129.7 (CH), 128.8 (2 x CH), 127.7 (CH), 127.7 (CH_2), 125.8 (2 x CH), 96.1 (C), 71.3 (CH_2), 61.1 (CH), 25.2 (CH_3), 23.2 (CH_3). These spectral data are consistent with those reported previously.[76]

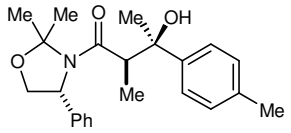
Cobalt-Catalyzed Reductive Aldol Reactions of *N*-Acryloyloxazolidine 225e With Various Ketones: General Procedure C



A solution of the *N*-alkenoyloxazolidine **225e** (231 mg, 1.00 mmol), the appropriate ketone (1.10 mmol) and $Co(acac)_2{\cdot}2H_2O$ (12.9 mg, 0.05 mmol) in THF (5.0 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 2.00 mL, 2.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (30 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the aldol product.

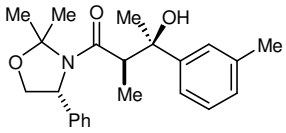


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (230a). The title compound was prepared according to General procedure **C** from acetophenone (130 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (257 mg, 73%). Recrystallisation of a CH_2Cl_2/hexane solution of **230a** at -20 °C was found to give colourless crystals suitable for X-ray diffraction. m.p. 215-217 °C; $[\alpha]_D^{21}$ –231 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3388 (OH), 2980, 2933, 2878, 1624 (C=O), 1458, 1420, 1065, 765, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53-7.48 (2H, m, Ar**H**), 7.47-7.42 (3H, m, Ar**H**); 7.23-7.12 (3H, m, Ar**H**), 6.94 (2H, app d, *J* = 7.2 Hz, Ar**H**), 5.48 (1H, br s, O**H**), 4.77 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.60 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.67 (3H, s, C(C**H**$_3$)$_2$), 0.99 (3H, s, C**H**$_3$COH), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.8 (C), 142.0 (C), 129.2 (2 x CH), 128.5 (CH), 127.8 (2 x CH), 126.7 (2 x CH), 126.1 (CH), 124.5 (2 x CH), 96.3 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2064, found: 354.2064.

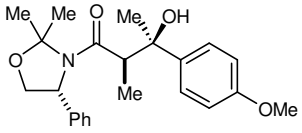


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(4-methylphenyl) butanoyl]-2,2-dimethyl-4-phenyloxazolidine (230b). The title compound was prepared according to General procedure **C** from 4′-methylacetophenone (155 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (280 mg, 76%). m.p. 171-173 °C; $[\alpha]_D^{21}$ –249 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2985, 2932, 1621 (C=O), 1458, 1423, 1377, 1303, 1205, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.48 (2H, m, Ar**H**), 7.46-7.41 (3H, m, Ar**H**), 7.03-7.01 (2H, m, Ar**H**), 6.82 (2H, d, *J* = 7.9 Hz, Ar**H**), 5.43 (1H, s, O**H**), 4.77 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.58 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.29 (3H, s, ArC**H**$_3$), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.67 (3H, s, C(C**H**$_3$)$_2$), 0.98 (3H, s, C**H**$_3$COH), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 142.9 (C), 142.0 (C), 135.6 (C), 129.1 (2 x

CH), 128.5 (3 x CH), 126.7 (2 x CH), 124.4 (2 x CH), 96.2 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.7 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 20.9 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2218.

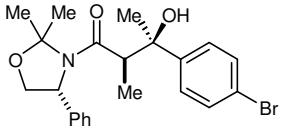


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-(3-methylphenyl) butanoyl]-2,2-dimethyl-4-phenyloxazolidine (230c). The title compound was prepared according to General procedure **C** from 3′-methylacetophenone (150 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (278 mg, 72%). m.p. 95-97 °C; $[\alpha]_D^{21}$ –199 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2980, 2933, 2878, 1624 (C=O), 1419, 1302, 1066, 845, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.49 (2H, m, Ar**H**), 7.47-7.43 (3H, m, Ar**H**), 7.09 (1H, t, *J* = 7.7 Hz, Ar**H**), 6.96 (1H, d, *J* = 7.7 Hz, Ar**H**), 6.75-6.73 (2H, m, Ar**H**), 5.41 (1H, s, O**H**), 4.78 (1H, dd, J = 6.6, 2.2 Hz, C$\mathbf{H}_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, C$\mathbf{H}_2$O), 2.61 (1H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}$), 2.28 (3H, s, ArC$\mathbf{H}_3$), 1.99 (3H, s, C(C$\mathbf{H}_3$)$_2$), 1.67 (3H, s, C(C$\mathbf{H}_3$)$_2$), 0.99 (3H, s, C$\mathbf{H}_3$COH), 0.91 (3H, d, *J* = 7.1 Hz, C$\mathbf{H}_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.7 (C), 142.0 (C), 137.2 (C), 129.1 (2 x CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 126.7 (2 x CH), 125.2 (CH), 121.5 (CH), 96.1 (C), 74.6 (C), 70.9 (CH_2), 61.6 (CH), 46.6 (CH), 29.6 (CH_3), 25.5 (CH_3), 22.6 (CH_3), 21.5 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2221, found: 368.2230.

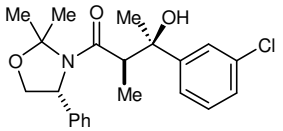


(4*R*)-3-[(2*R*,3*R*)-3-Hydroxy-3-(4-methoxyphenyl)-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (230d). The title compound was prepared according to General procedure **C** from 4′-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (274 mg, 72%). Recrystallisation of an EtOAc/hexane solution of **230d** at -20 °C was found to give colourless crystals suitable for X-ray diffraction. m.p. 183-185 °C; $[\alpha]_D^{21}$ –222 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3366 (OH), 2984, 2971, 2928, 1617 (C=O), 1510, 1250, 1177, 1065, 841 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.47 (2H, m, Ar**H**), 7.46-7.42 (3H, m, Ar**H**), 6.85 (2H, d, *J* = 8.7 Hz, Ar**H**),

6.75-6.73 (2H, m, Ar**H**), 5.44 (1H, br s, O**H**), 4.77 (1H, dd, *J* = 6.6, 2.1 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.1 Hz, C**H**$_2$O), 3.76 (3H, s, OC**H**$_3$), 2.54 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**), 1.98 (3H, s, C(C**H**$_3$)$_2$), 1.66 (3H, s, C(C**H**$_3$)$_2$), 0.97 (3H, s, C**H**$_3$COH), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 157.9 (C), 142.0 (C), 138.0 (C), 129.1 (2 x CH), 128.5 (CH), 126.7 (2 x CH), 125.6 (2 x CH), 113.1 (2 x CH), 96.2 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 55.1 (CH_3), 46.8 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_4$ $[M+H]^+$: 384.2169, found: 384.2167.

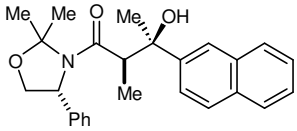


(4R)-3-[(2R,3R)-3-(4-Bromophenyl)-3-hydroxy-2-methyl butanoyl]-2,2-dimethyl-4-phenyloxazolidine (230e). The title compound was prepared according to General procedure **C** from 4′-bromoacetophenone (219 mg, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (273 mg, 63%). m.p. 132-134 °C; $[\alpha]_D^{21}$ –236 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2933, 2878, 1625 (C=O), 1457, 1411, 1066, 840, 703 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.52-7.40 (5H, m, Ar**H**), 7.33-7.31 (2H, m, Ar**H**), 6.79 (2H, d, *J* = 8.3 Hz, Ar**H**), 5.48 (1H, s, O**H**), 4.75 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.53 (1H, q, *J* = 7.1 Hz, CH$_3$C**H**), 1.97 (3H, s, C(C**H**$_3$)$_2$), 1.66 (3H, s, C(C**H**$_3$)$_2$), 0.96 (3H, s, C**H**$_3$COH), 0.88 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.9 (C), 144.9 (C), 141.9 (C), 130.8 (2 x CH), 129.2 (2 x CH), 128.6 (CH), 126.7 (2 x CH), 126.5 (2 x CH), 120.1 (C), 96.3 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 46.5 (CH), 29.4 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{27}{}^{79}BrNO_3$ $[M+H]^+$: 432.1169, found: 432.1168.

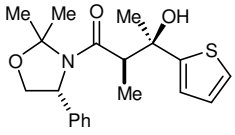


(4R)-3-[(2R,3R)-3-(4-Bromophenyl)-3-hydroxy-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (230f). The title compound was prepared according to General procedure **C** from 3′-chloroacetophenone (143 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a colourless

oil (225 mg, 58%). $[\alpha]_D^{21}$ –162 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2934, 2877, 1627 (C=O), 1419, 1205, 1066, 842, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.49 (2H, m, Ar**H**), 7.48-7.42 (3H, m, Ar**H**), 7.15-7.10 (2H, m, Ar**H**), 6.89-6.83 (2H, m, Ar**H**), 5.45 (1H, s, O**H**), 4.75 (1H, dd, *J* = 6.7, 2.2 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.7 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.58 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.97 (3H, s, C(C**H**$_3$)$_2$), 1.66 (3H, s, C(C**H**$_3$)$_2$), 0.93 (3H, s, C**H**$_3$COH), 0.89 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.8 (C), 148.0 (C), 141.9 (C), 133.9 (C), 129.3 (2 x CH), 129.1 (CH), 128.6 (CH), 126.7 (2 x CH), 126.3 (CH), 1245.0 (CH), 122.7 (CH), 96.2 (C), 74.4 (C), 70.9 (CH_2), 61.7 (CH), 46.5 (CH), 29.4 (CH_3), 25.5 (CH_3), 22.7 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{27}{}^{35}ClNO_3$ $[M+H]^+$: 388.1675, found: 388.1675.

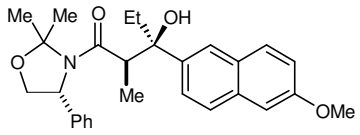


(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(naphthalen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (230g). The title compound was prepared according to General procedure **C** from 2′-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (302 mg, 75%). m.p. 215-217 °C; $[\alpha]_D^{21}$ –11.2 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3410 (OH), 2980, 2933, 2878, 1624 (C=O), 1456, 1418, 1377, 1299, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.78-7.76 (2H, m, Ar**H**), 7.67 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.61-7.40 (8H, m, Ar**H**), 6.86-6.84 (1H, m, Ar**H**), 5.59 (1H, br s, O**H**), 4.80 (1H, dd, *J* = 6.6, 2.2 Hz, C**H**$_2$O), 4.42 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 4.01 (1H, dd, *J* = 9.1, 2.2 Hz, C**H**$_2$O), 2.74 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.02 (3H, s, C(C**H**$_3$)$_2$), 1.69 (3H, s, C(C**H**$_3$)$_2$), 1.09 (3H, s, C**H**$_3$COH), 0.91 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 143.2 (C), 142.1 (C), 133.1 (C), 132.0 (C), 129.3 (2 x CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 126.8 (2 x CH), 125.8 (CH), 125.4 (CH), 123.5 (CH), 122.8 (CH), 96.3 (C), 74.9 (C), 71.0 (CH_2), 61.7 (CH), 46.6 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{30}NO_3$ $[M+H]^+$: 404.2220, found: 404.2221.



(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(thiophen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (230h). The

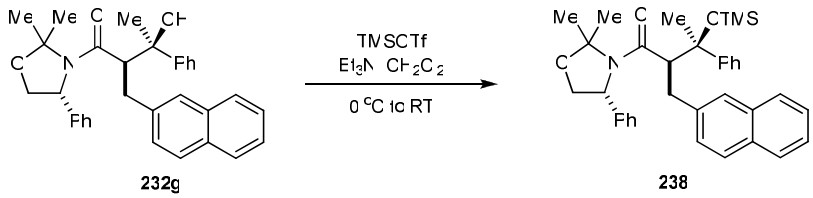
title compound was prepared according to General procedure **C** from 2-acetylthiophene (119 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH_2Cl_2/hexane to give a white solid (220 mg, 61%). m.p. 143-145 °C; $[\alpha]_D^{21}$ –11.8 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3399 (OH), 2983, 2933, 2878, 1625 (C=O), 1422, 1237, 1066, 844, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50-7.39 (5H, m, Ar**H**), 7.09 (1H, dd, *J* = 5.1, 1.2 Hz, C**H**), 6.86 (1H, dd, *J* = 5.1, 3.5 Hz, C**H**), 6.35 (1H, dd, *J* = 3.5, 1.2 Hz, C**H**), 5.57 (1H, s, O**H**), 4.76 (1H, dd, *J* = 6.6, 2.1 Hz, C**H**$_2$O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.1 Hz, C**H**$_2$O), 2.60 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 1.96 (3H, s, C(C**H**$_3$)$_2$), 1.65 (3H, s, C(C**H**$_3$)$_2$), 1.04 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH), 1.00 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.8 (C), 151.0 (C), 141.8 (C), 129.1 (2 x CH), 128.4 (CH), 126.6 (2 x CH), 126.5 (CH), 123.1 (CH), 121.0 (CH), 96.2 (C), 74.7 (C), 70.9 (CH_2), 61.5 (CH), 47.7 (CH), 30.6 (CH_3), 25.5 (CH_3), 22.6 (CH_3), 12.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_3S$ $[M+H]^+$: 360.1628, found: 360.1637.



(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(thiophen 2yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (230j). The title compound was prepared according to General procedure **C** from 6′-methoxy-2′-propiononaphthone (236 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH_2Cl_2/hexane to give a white solid (265 mg, 59%). m.p. 164-166 °C; $[\alpha]_D^{21}$ –3.9 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3388 (OH), 2975, 2935, 2877, 1623 (C=O), 1417, 1266, 1173, 1067, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.58-7.45 (7H, m, Ar**H**), 7.12 (1H, dd, *J* = 8.9, 5.6 Hz, Ar**H**), 7.08 (1H, d, *J* = 2.5 Hz, Ar**H**), 5.21 (1H, s, O**H**), 4.79 (1H, dd, *J* = 6.6, 2.1 Hz, C**H**$_2$O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C**H**N), 3.99 (1H, dd, *J* = 9.1, 2.1 Hz, C**H**$_2$O), 3.91 (3H, s, OC**H**$_3$), 2.67 (1H, q, *J* = 7.1 Hz, CH_3C**H**), 2.00 (3H, s, C(C**H**$_3$)$_2$), 1.67 (3H, s, C(C**H**$_3$)$_2$), 1.65-1.55 (1H, m, C**H**$_2$CH$_3$), 0.96-0.85 (1H, m, C**H**$_2$CH$_3$), 0.90 (3H, d, *J* = 7.1 Hz, C**H**$_3$CH), 0.43 (3H, t, *J* = 7.3 Hz, CH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.5 (C), 157.3 (C), 142.1 (C), 138.6 (C), 132.9 (C), 129.5 (CH), 129.2 (2 x CH), 128.5 (CH and C), 126.7 (2 x CH), 126.2 (CH),

124.5 (CH), 123.7 (CH), 118.5 (CH), 105.3 (CH), 96.2 (C), 77.9 (C), 71.0 (CH_2), 61.6 (CH), 55.2 (CH_3), 46.8 (CH), 33.3 (CH_2), 25.7 (CH_3), 22.6 (CH_3), 12.3 (CH_3), 7.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{28}H_{34}NO_4$ $[M+H]^+$: 448.2483, found: 448.2490.

1-((*R*)-2,2-Dimethyl-4-phenyl-oxazolidin-3-yl)-2-naphthalen-2-ylmethyl-3-phenyl-3-trimethylsilanyloxy-butan-1-one (238).



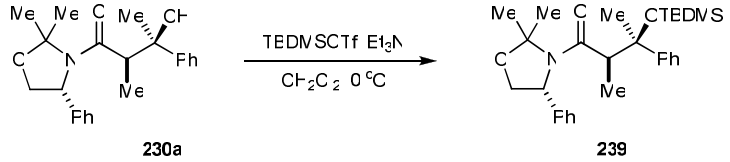
232g 238

To a stirred solution of aldol product **232g**[i] (402 mg, 0.84 mmol), and Et_3N (234 µL, 1.68 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added trimethylsilyltriflate (212 µL, 1.174 mmol) dropwise over 5 min. The reaction was stirred at 0 °C for a further 15 min and then at room temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the silyl protected product **238** (430 mg, 95%) as a colourless oil that was used without further purification; $[\alpha]_D^{21}$ –118.2 (*c* 1.02, $CHCl_3$); IR (film) 2983, 1651 (C=O), 1255, 1402, 1374, 1362, 1301, 1249, 1167, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.79-7.72 (1H, m, Ar**H**), 7.68-7.64 (1H, m, Ar**H**), 7.48-7.41 (3H, m, Ar**H**), 7.35-7.20 (5H, m, Ar**H**), 7.15-7.10 (4H, m, Ar**H**), 6.80-6.77 (3H, m, Ar**H**), 3.46 (1H, dd, *J* = 8.8, 6.5 Hz, OCH_2CHN), 3.29-3.27 (1H, m, $PhCH_2CH$), 3.14-3.12 (1H, m, $PhCH_2CH$), 3.08-3.05 (1H, m, $PhCH_2CH$), 2.89-2.86 (1H, dd, *J* = 12.7, 2.5 Hz, OCH_2CHN), 2.78-2.75 (1H, dd, *J* = 11.7, 2.5 Hz, OCH_2CHN), 1.67 (3H, s, CH_3C), 1.59 (3H, s, CH_3), 1.56 (3H, s, CH_3), 0.14 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.9 (C), 145.0 (C), 142.6 (C), 140.8 (C), 132.8 (C), 132.0 (C), 129.4 (2 x CH), 128.7 (2 x CH), 128.4 (3 x CH), 127.6 (CH), 127.2 (CH), 126.9 (CH), 126.5 (CH), 126.4 (2 x CH), 125.4 (2 x CH), 124.4 (CH), 124.1 (CH), 95.9 (C), 78.9 (C), 70.7 (CH_2), 60.3

[i] **232g** prepared by Pekka M. Joensuu

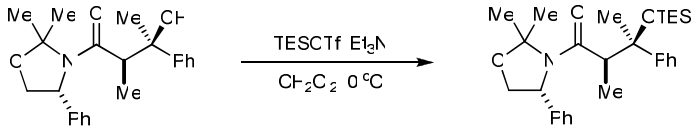
(CH), 59.3 (CH), 35.4 (CH_2), 26.2 (CH_3), 25.4 (CH_3), 22.2 (CH_3), 2.5 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{35}H_{42}NO_3Si$ $[M+H]^+$: 552.2928, found: 552.2933.

3-(*t*-Butyl-dimethyl-silanyloxy)-1-((*R*)-2,2-dimethyl-4-phenyl-oxazolidin-3-yl)-2-methyl-3-phenyl-butan-1-one (239).



To a stirred solution of aldol product **230a** (200 mg, 0.57 mmol), and Et_3N (158 µL, 1.13 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added t-butyldimethylsilyltriflate (255 µL, 0.96 mmol) dropwise over 5 min. The reaction was stirred at 0 °C 2 h, quenched with saturated aqueous $NaHCO_3$ solution (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the silyl protected product **239** (263 mg, 99%) as a colourless oil; $[\alpha]_D^{21}$ – 29.1 (*c* 1.03, $CHCl_3$); IR (film) 2929, 2856, 1655 (C=O), 1456, 1403, 1362, 1248, 1121, 1070, 1022 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.32 (3H, m, Ar**H**), 7.14-7.10 (2H, m, Ar**H**), 7.06-7.01 (1H, m, Ar**H**), 6.96-6.91 (2H, m, Ar**H**), 6.75-6.72 (2H, m, Ar**H**), 4.62 (1H, dd, *J* = 6.4, 1.3 Hz, OC**H**$_2$CHN), 4.24 (1H, dd, *J* = 8.9, 6.5 Hz, OCH_2C**H**N), 3.81 (1H, dd, *J* = 8.9, 1.3 Hz, OC**H**$_2$CHN), 2.78 (1H, q, *J* = 7.2 Hz, CH_3C**H**), 1.75 (3H, s C**H**$_3$CO), 1.55 (3H, s, C**H**$_3$C), 1.47 (3H, s, C**H**$_3$), 1.29 (3H, d, *J* = 7.2 Hz, C**H**$_3$CH), 0.86 (9H, s, SiC(C**H**$_3$)$_3$), -0.01 (3H, s, SiC**H**$_3$), -0.44 (3H, s, SiC**H**$_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 172.5 (C), 146.6 (C), 142.5 (C), 129.0 (2 x CH), 127.7 (CH), 127.1 (2 x CH), 126.8 (2 x CH), 126.2 (2 x CH), 125.8 (CH), 95.6 (C), 77.2 (C), 71.1 (CH_2), 61.4 (CH), 50.9 (CH), 26.1 (3 x CH_3), 25.4 (CH_3), 23.7 (CH_3), 22.4 (CH_3), 18.4 (C), 12.5 (CH_3), -1.9 (CH_3), -3.1 (CH_3); HRMS (EI) Exact mass calcd for $C_{28}H_{42}NO_3Si$ $[M+H]^+$: 468.2929, found: 468.2931.

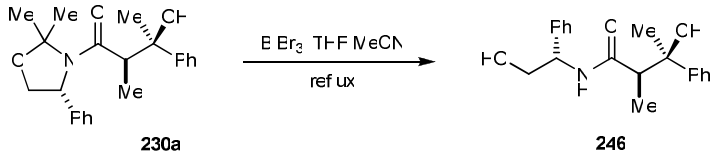
1-((R)-2,2-Dimethyl-4-phenyl-oxazolidin-3-yl)-2-methyl-3-phenyl-3-triethyl silanyloxy-butan-1-one (241).



230a 241

To a stirred solution of aldol product **230a** (200 mg, 0.57 mmol), Et_3N (158 μL, 1.13 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylsilyltriflate (192 μL, 0.85 mmol) dropwise over 5 min. The reaction was stirred at 0 °C for a further 15 min, quenched with saturated aqueous $NaHCO_3$ solution (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→25% EtOAc/hexane) afforded the silyl protected product **241** (266 mg, 99%) as a colourless oil. $[\alpha]_D^{21}$ –68.6 (*c* 1.02, $CHCl_3$); IR (film) 2953, 2874, 1655 C=O), 1495, 1456, 1404, 1362, 1236, 1123, 1070 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.29 (3H, m, Ar**H**), 7.07-7.03 (3H, m, Ar**H**), 6.96-6.93 (2H, m, Ar**H**), 6.77-6.75 (2H, m, Ar**H**), 4.63-4.62 (1H, m, $OCH_2C\mathbf{H}N$), 4.24 (1H, dd, *J* = 9.0, 6.5 Hz, $OC\mathbf{H}_2CHN$), 3.80-3.78 (1H, m, $OC\mathbf{H}_2CHN$), 2.71 (1H, q, *J* = 7.1 Hz, $C\mathbf{H}CH_3$), 1.74 (3H, s, $C\mathbf{H}_3C$), 1.55 (3H, s, $C\mathbf{H}_3$), 1.50 (3H, s, $C\mathbf{H}_3$), 1.28 (3H, d, *J* = 7.1 Hz, $C\mathbf{H}_3CH$), 0.80 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 0.51-0.31 (6H, m, $Si(C\mathbf{H}_2CH_3)_3$); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 172.6 (C), 147.1 (C), 142.4 (C), 128.9 (2 x CH), 127.6 (CH), 127.1 (2 x CH), 126.6 (2 x CH), 126.1 (2 x CH), 125.8 (CH), 95.6 (C), 77.4 (C), 71.2 (CH_2), 61.3 (CH), 51.1 (CH), 25.4 (CH_3), 23.7 (CH_3), 22.5 (CH_3), 12.6 (CH_3), 7.1 (3 x CH_3), 6.5 (3 x CH_2); HRMS (ES) Exact mass calcd for $C_{28}H_{42}NO_3Si$ $[M+H]^+$: 468.2928, found: 468.2931.

3-Hydroxy-*N*-((R)-2-hydroxy-1-phenyl-ethyl)-2-methyl-3-phenyl-butyramide (246).

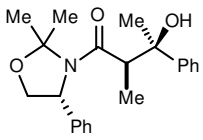


230a **246**

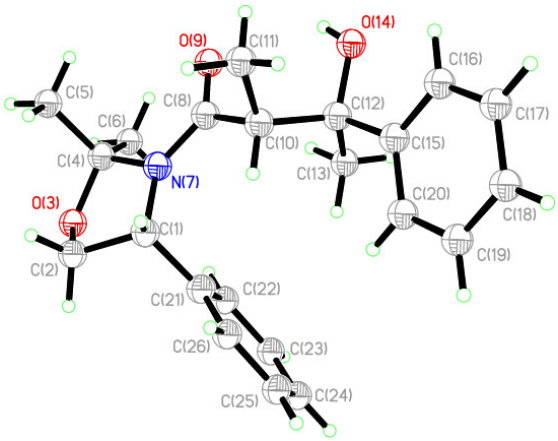
To a solution of aldol product **230a** (500mg, 1.40 mmol) in THF (2.5 mL) and MeCN (2.5 mL) was added $BiBr_3$ (1.27 g, 5.60 mmol) under open flask conditions. The mixture was heated to reflux for 24 h after which NaHCO3 (10 mL) was added and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→50% EtOAc/hexane) afforded the secondary amide product **246** (154 mg, 35%) as an off-white solid. m.p. 154 - 156 °C; $[\alpha]_D^{21}$ – 51.9 (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 1627 (C=O), 1540, 1448, 1357, 1182, 909, 830, 765, 697, 609 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45-7.22 (10H, m, Ar**H**), 5.59 (1H, s, CO**H**), 5.13 (1H, m, PhC**H**NH), 4.59 (1H, s, **H**OCH_2), 3.97-3.88 (2H, m, HOC**H**$_2$), 2.61 (1H, q, *J* = 7.0 Hz, CH_3C**H**), 2.38 (1H, s, N**H**), 1.63 (3H, s, CC**H**$_3$), 0.98 (3H, d, *J* = 7.0 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 177.1 (C), 145.5 (C), 138.5 (C), 129.0 (2 x CH_2), 128.1 (2 x CH_2), 126.5 (2 x CH_2), 124.8 (2 x CH_2), 74.7 (C), 55.5 (CH), 50.6 (CH), 29.7 (CH_3), 13.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1755, found: 314.1751.

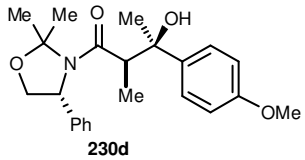
Stereochemical Determinations

The relative stereochemistries of **230a** and **230d** were determined by X-ray crystallography.

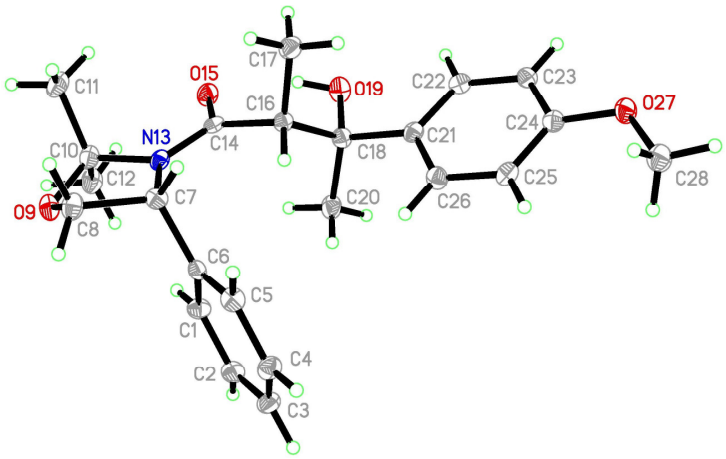


230a





230d



The relative stereochemistries of the remaining products **230b-j** were assigned by analogy.

3.6 References

[67] Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

[68] a) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631. (b) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645–8658. For the use of chiral oxazolidines in related reactions, see: (c) Lettan, R. B., II; Reynolds. T. E.; Galliford, C. V.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15566. (d) Lettan, R. B., II; Woodward, C. C.; Scheidt, K. A. *Angew. Chem.*, *Int. Ed.* **2008**, *47*, 2294.

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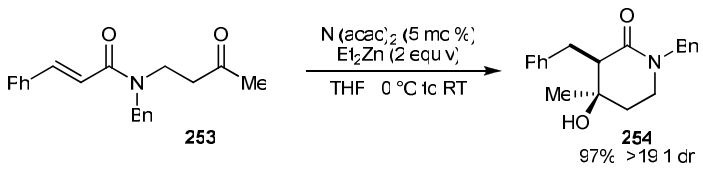
4 Literature Review of Formal Homoaldol Cyclisation Reactions

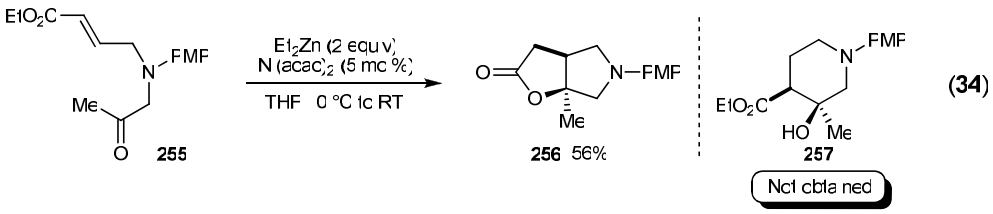
4.1 Introduction

Previously within our group, a novel catalytic reductive aldol cyclisation methodology catalysed by $Ni(acac)_2$ with a stoichiometric amount of diethylzinc had been developed. A representative example is shown in Eq 33.[78]



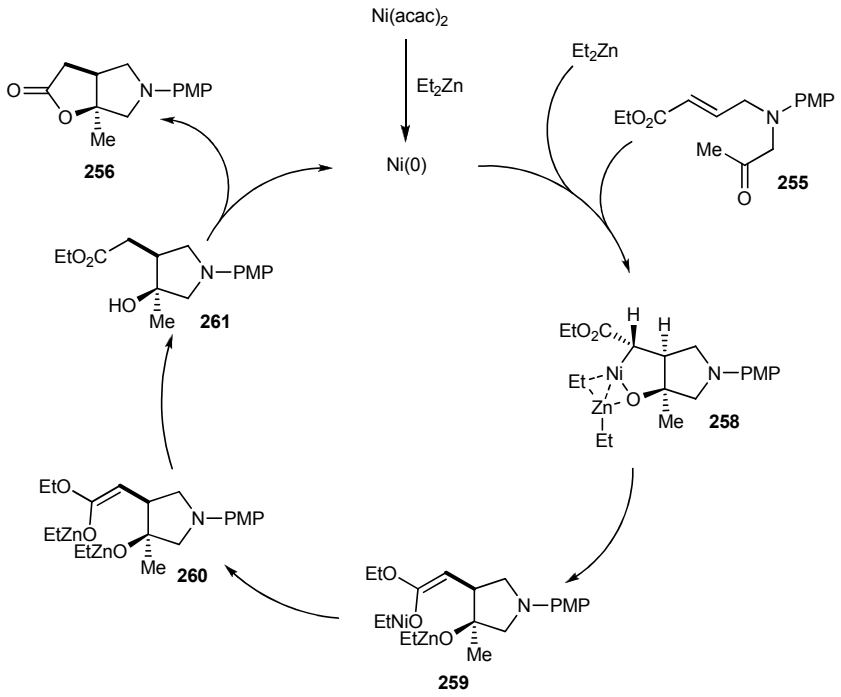
(33)

Treatment of substrate **253**, containing an α,β-unsaturated carbonyl tethered to a ketone via an amide linkage, with $Ni(acac)_2$ and Et_2Zn leads to the formation of β-hydroxylactam **254** in excellent yield and diastereoselectivity. This cyclisation work is more thoroughly described on page 48. However, it was during efforts to gain mechanistic insights into these reactions that another discovery was made. Substrate **255**, where the α,β-unsaturated carbonyl is tethered to the ketone through the γ-carbon, was prepared and cyclised (Eq 34).



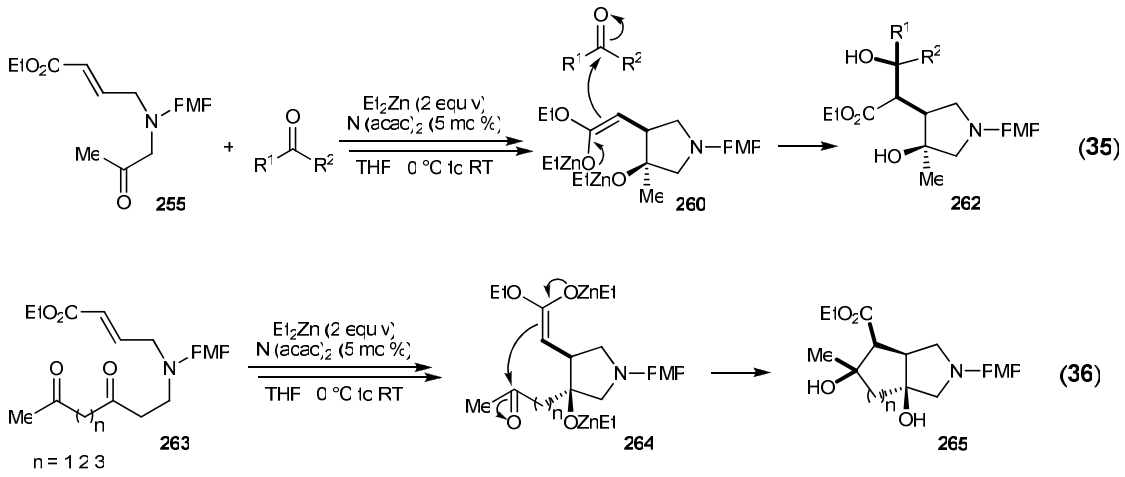
(34)

Instead of providing the expected reductive aldol product **257**, the bicyclic lactone **256** was obtained in 56% yield. It was postulated that a metallacycle pathway is most likely responsible for this formal reductive *homo*aldol reaction. A proposed mechanism for this reaction is presented in Scheme 27.



Scheme 27: Proposed Mechanism of Bicyclic Lactone 256 Formation

Treatment of $Ni(acac)_2$ with Et_2Zn leads to a rapid reduction to form Ni(0). Oxidative cyclisation of Ni(0) with both the alkene and the ketone of **255** would result in oxanickellacycle **258**. Cleavage of the oxanickellacyle **258** by transmetallation with Et_2Zn provides nickel enolate **259**, which after further transmetallation with Et_2Zn provides zinc enolate **260**. Workup of the reaction mixture furnishes hydroxyester **261**, which upon spontaneous lactonisation provides bicyclic lactone **256**. In this mechanism, the zinc enolate **260** is protonated. Rather than protonation, we questioned whether the reactivity inherent in enolate **260** might be harnessed in a further carbon-carbon bond forming reaction either in an intermolecular reaction (Eq 35) or in a second intramolecular reaction (Eq 36).



Double cyclisation reactions of the type illustrated in Eq 36 would allow the formation of two fused rings and the potential to create up to four or more contiguous stereocentres, all in one step. If the stereochemistry of such reactions can be controlled, then the potential exists to develop methodologies that allow access to highly functionalised polycyclic building blocks, prerequisites for many natural products including scopadulcic acid A (**266**) and anistatin A (**267**) (Figure 8).

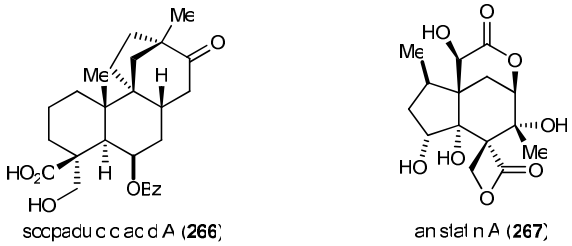


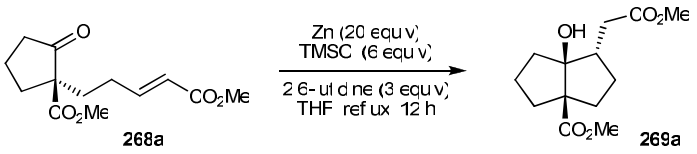
Figure 8: Natural Products Containing Densely Functionalised Fused Rings

4.2 Literature precedents

At this point it is worth examining the related work of other groups in the field. Presented first are a number of formal homoaldol reactions mediated by various metals, the products of which are obtained via a radical mechanism. Following this discussion, the current state in the field of polycyclisation reactions catalysed by nickel will be discussed.

4.2.1 Zinc-Trimethylchlorosilane-Mediated Radical Cyclisations

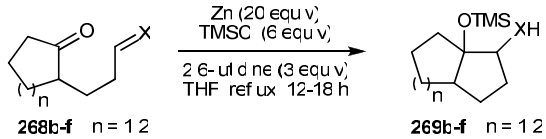
In 1983, Corey and Pyne reported a novel methodology for the formation of cyclopentanols.[79] Zinc-triethylchlorosilane was used to mediate radical reactions between a ketone and a tethered α,β-unsaturated ester in a formal intramolecular homoaldol reaction (Eq 37).

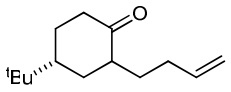
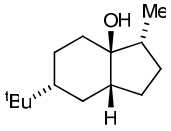
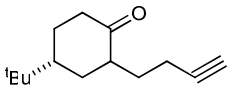
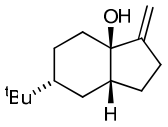
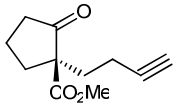
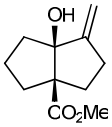
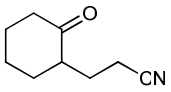
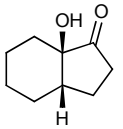
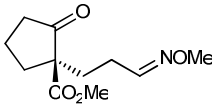
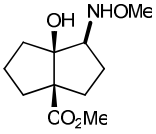


(37)

The methodology was also applicable to a range of other substrates as illustrated in Table 35.

Table 35: Zinc-trimethylchlorosilane Mediated Radical Cyclisations



Entry	Substrate		Product[a]		Yield(%)
1		**268b**		**269b**	66%
2		**268c**		**269c**	74%
3		**268d**		**269d**	77%
4		**268e**		**269e**	78%
5		**268f**		**269f**	84%

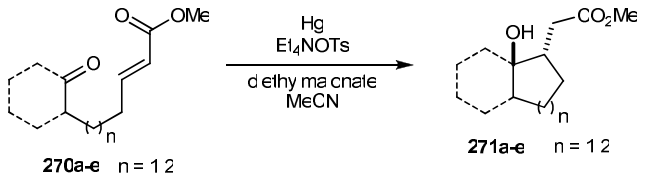
a) All products isolated as a single diastereomer

Substrates containing a wide range of substitution underwent cyclisation to give cyclopentanols in good yields as single diastereomers. The requirement for a δ-ε-π functionality can be achieved with alkenes (entry 1), alkynes (entries 2 and 3), nitriles (entry 4) and even methoximes (entry 5).

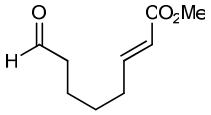
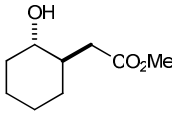
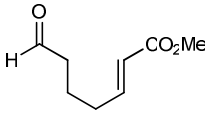
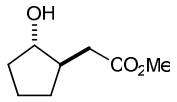
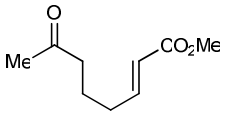
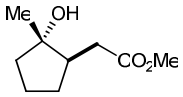
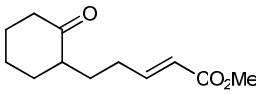
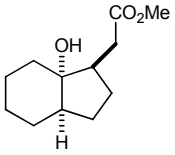
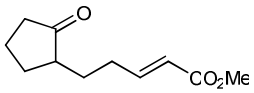
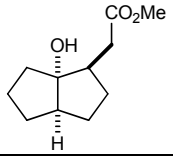
4.2.2 Electroreductive Radical Cyclisations

In 1985, Little and co-workers reported an electroreductive cyclisation methodology for the cyclisation of α,β-unsaturated esters tethered to a ketone via a carbon chain.[80] This formal homoaldol reaction uses mercury electrodes, together with diethylmalonate as the proton source (Table 36).

Table 36: Electroreductive Cyclisations of α,β-Unsaturated Esters Tethered to Ketones and Aldehydes



270a-e n = 1 2 271a-e n = 1 2

Entry	Substrate		Product[a]		dr (trans/cis)[b]	Yield(%)
1		**270a**		**271a**	1.8:1	72%
2		**270b**		**271b**	1.4:1	70%
3		**270c**		**271c**	5.1:1	76%
4		**270d**		**271d**	2.5:1	74%
5		**270e**		**271e**	11.4:1	79%

a) The major trans products are illustrated b) trans product (ie., trans-OH and ester groups)

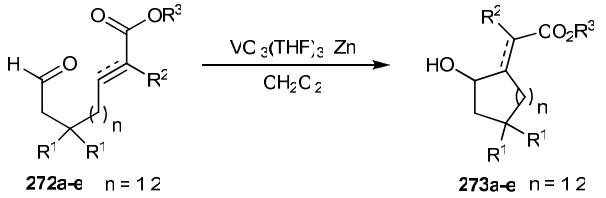
A range of substrates were cyclised to provide five- and six-membered hydroxyesters in good yield with diastereoselectivity ranging from poor to good. Both aldehydes (entries 1 and 2) and ketones (entries 3-5) serve as competent substrates. In addition, cyclic ketones can be utilised to provide fused six-five-membered rings (entry 4) and fused five-five-membered ring products (entry 5).

4.2.3 Vanadium Mediated Radical Cyclisations

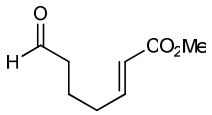
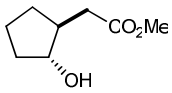
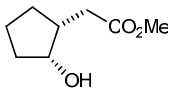
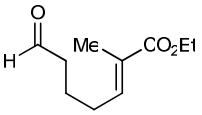
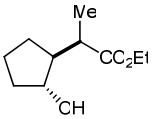
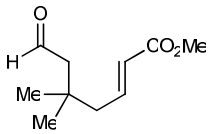
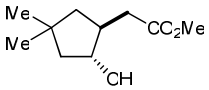
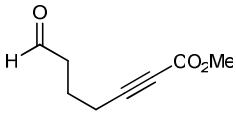
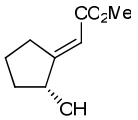
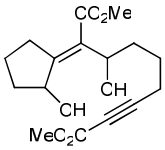
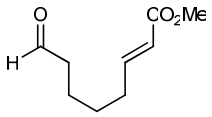
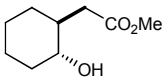
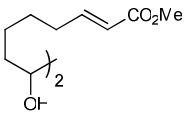
In 1991, Torii and co-workers reported a vanadium(II) mediated formal homo aldol cyclisation of enals and ynals.[81] Using $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ which was prepared

from reduction of $VCl_3(THF)_3$ with Zn, smooth cyclisation was achieved and in some cases, very high diastereoselectivity was achieved (Table 37).

Table 37: Vanadium(II) Mediated Cyclisation of Enals and Ynals Tethered to Aldehydes



272a-e n = 1 2 **273a-e** n = 1 2

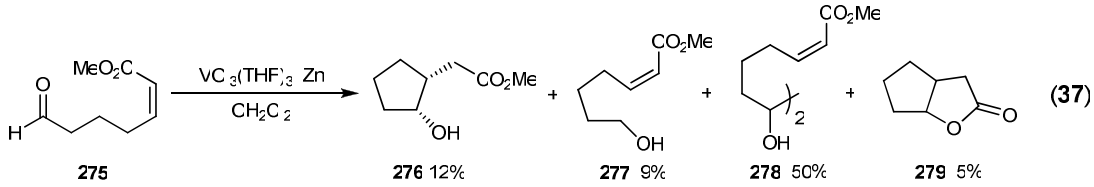
Entry	Substrate	Product	Side Product	Yield(%)product (side-product)[a]
1	 **272a**	 **273a**	 **274a**	68%[b]
2	 **272b**	 **273b**	-	77%[c]
3	 **272c**	 **273c**	-	67%[c]
4[d]	 **272d**	 **273d**	 **274d**	55(45)%
5	 **272e**	 **273e**	 **274e**	45(46)%

a) The yields for the desired product are given. Yields of side products when obtained are given in parentheses. b) The diastereoselectivity was found to be 24:1 in favour of the trans product. The minor cis product was not isolated. c) Cis diastereomer not detected by ^{1}H NMR spectroscopic analysis. d) Reaction performed in THF.

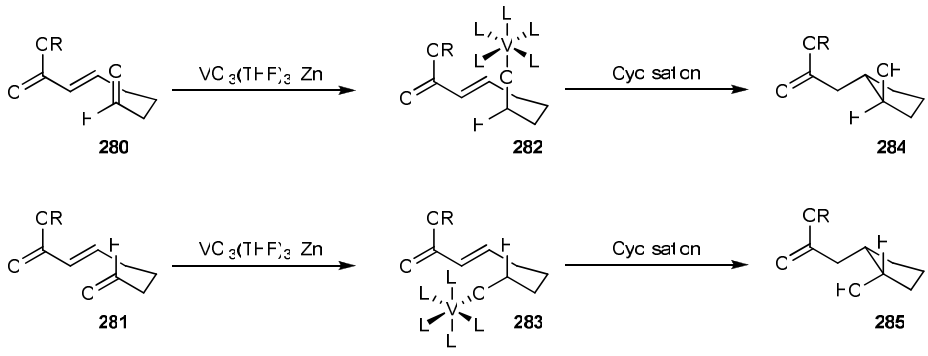
Cyclisation of substrate **272a** afforded the desired trans product **273a** in 68% yield and with a diastereoselectivity of 24:1 (entry 1). Even higher levels of trans-selectivity were obtained when the methacrylate derivative **272b** and the substrate **272c** were cyclised, where the cis product was not observed by ^{1}H NMR spectroscopic analysis (entries 2 and 3). The reaction conditions were also applicable

to substrates containing triple bonds. Substrate **272d** was successfully cyclised in 55% yield although the dimeric product **274d** was also isolated in 45% yield (entry 4). In addition, access to six-membered rings was achieved with the cyclisation of **272e** to form the cyclohexanol **273e**, although the pinacol side product **274e** was also isolated in 46% yield (entry 5).

In order to understand the trans selectivity observed in the reaction of the *E* olefin **272a**, the reductive coupling of the *Z* olefin **275** was examined (Eq 37).



Cyclisation of **275** afforded the pinacol **278** as the major product isolated in 50% yield. A mixture of the alcohol **277** (9%), the γ-lactone **279** (5%) as well as **276** (12%) was isolated. Torri suggested that the trapping of the *E* olefin could proceed via either vanadium aldehyde ketyl intermediates **282** or **283** (Scheme 28).



Scheme 28: Proposed Intermediates During Cyclisation

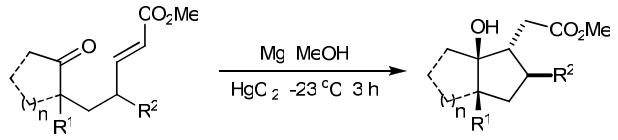
Based on the observed result with **275**, it was likely the *E* olefin mechanism proceeded via intermediate **282** leading to the formation of the trans product. In the case of **275**, the mechanism proceeded via an intermediate of the type **283** which lead

to considerable steric hindrance which in turn lead to the predominant formation of products derived from intermolecular reactions.

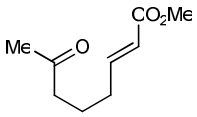
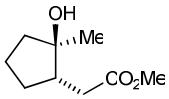
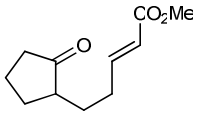
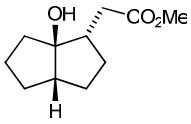
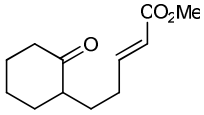
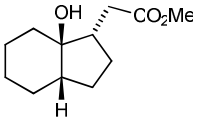
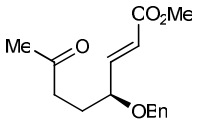
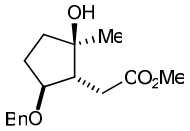
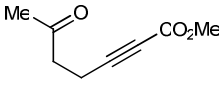
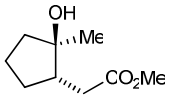
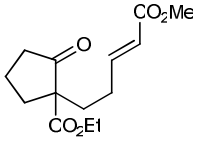
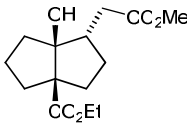
4.2.4 Magnesium Mediated Radical Cyclisations

In 1994 Lee, Pak and co-workers disclosed another reductive cyclisation of ketones tethered to activated olefins, this time mediated by magnesium in dry methanol and in the presence of mercuric chloride (Table 38).[82]

Table 38: Reductive Cyclisation of Ketones Tethered to α,β-Unsaturated Esters Mediated by Magnesium in Methanol



286a-f n = 1 2 **287a-f** n = 1 2

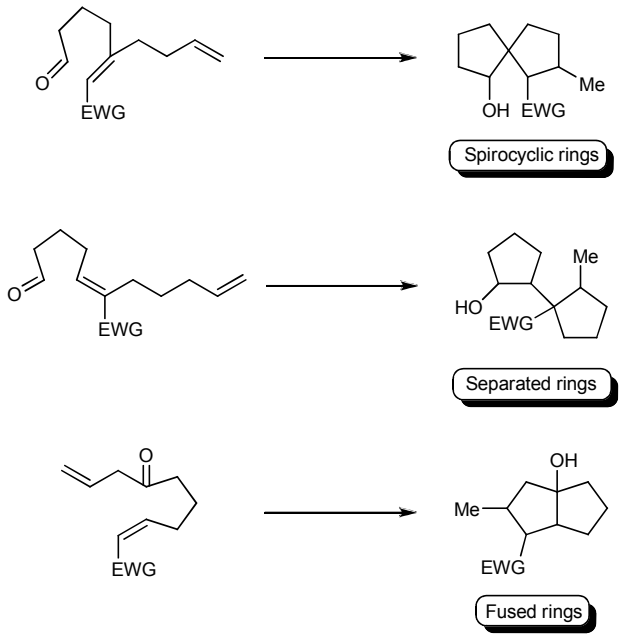
Entry	Substrate		Product[a]		dr (trans/cis)[b]	Yield(%)
1		**286a**		**287a**	4.32:1	98%
2		**286b**		**287b**	10.1:1	97%
3		**286c**		**287c**	1.12:1	98%
4		**286d**		**287d**	3.8:1	99%
5		**286e**		**287e**	4.32:1	95%
6		**286f**		**287f**	5.23:1	96%

a) The major trans products are illustrated b) trans product (ie., trans-OH and ester groups).

A range of substrates were successfully cyclised in very high yield and with moderate to high diastereoselectivity. The major product was always the trans isomer, and the cis isomer always lactonised under the reaction conditions. The reaction tolerates substitution with *O*-benzyl and ethyl ester groups (entries 4 and 6) as well as the presence of preformed rings (entries 2 and 3). In addition, an alkyne can be used, providing the same product as the equivalent α,β-unsaturated ester (entry 5). Attempts to cyclise aldehydes tethered to α,β-unsaturated esters in place of ketones only resulted in simple reduction of either the double bond or the aldehyde or both.

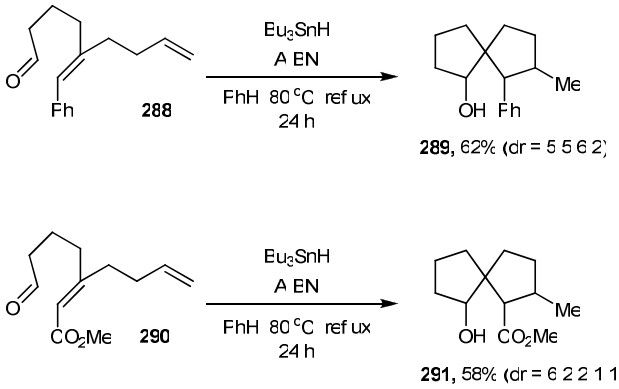
4.2.5 Tributyltin Hydride-Mediated Cyclisations

In 1997 Enholm and Burroff reported a novel tandem radical cyclisation reaction triggered by *O*-stannyl ketyl radicals using stoichiometric quantities of *n*-Bu_3SnH and the initiator AIBN.[83] Modification of both the positions and electronic properties of two olefins along with the length of a carbon tether in an acyclic precursor molecule allows access to a wide variety of bis-cyclopentanoid products (Scheme 29).



Scheme 29: Variation in Substrate Allowing Access to a Wide Variety of Cyclised Products

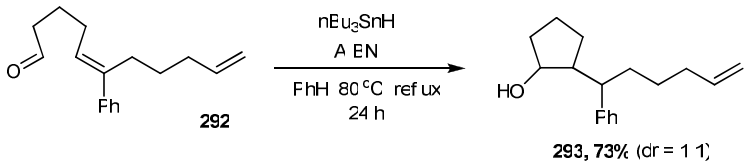
Enholm first attempted the synthesis of spirocylic type products and therefore substrates **288** and **290** were prepared and subjected to the reaction conditions (Eq 38).



(38)

Both aldehydes **288** and **290** provided the expected spiro-[4,4]-ring systems **289** and **291** in moderate yield with no monocyclic products being detected in either reaction. Using gas chromatographic analysis, the diastereomeric ratios were determined to be a disappointing 5:5:6:2 in the case of **289** and 6:2:2:1:1 in the case of **291**. In addition, these diastereomers were inseparable. However, these are still important results as they demonstrate that tandem cyclisations with substrates of the type **288** and **290** are possible.

Next, the synthesis of a 'separated' ring system was attempted and substrate **292** was subjected to the standard reaction conditions (Eq 39).



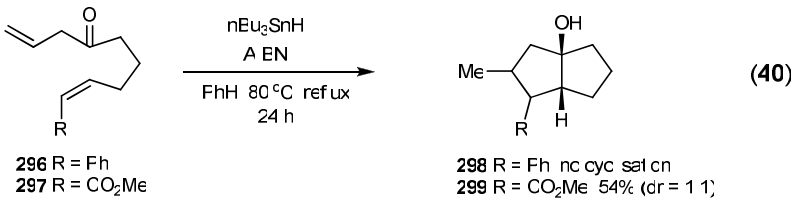
(39)

In this case, only the monocyclised product **293** was obtained as an inseparable mixture of diastereomers in the ratio 1:1. Enholm explained the difference in behaviour between the conversion of **288** to **289** and **292** to **293** by contrasting their intermediate carbon-centred radical species **294** and **295** (Figure 9).

Figure 9: Radical Intermediates Preceding Second Cyclisation

The pendant olefin in **294** has substantially reduced steric access to the radical centre, and so the 5-exo-trig transition state conformation is formed more slowly. Hydrogen atom transfer from tin hydride to **294** becomes faster than cyclisation and so the second ring does not form. In the 'spirocyclic' case, benzylic radical **295** has less difficulty approaching the olefin, because it is a secondary rather than a tertiary carbon-centred radical.

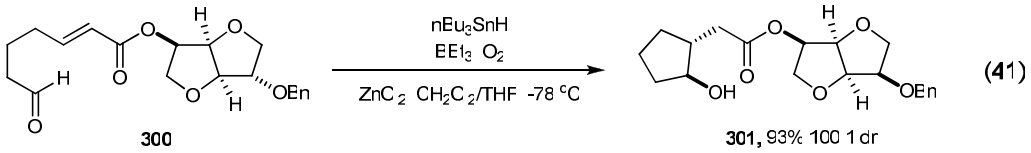
Next, substrates **296** and **297** were both prepared in order to cyclise a 'fused' type ring system (Eq 40).



(**40**)

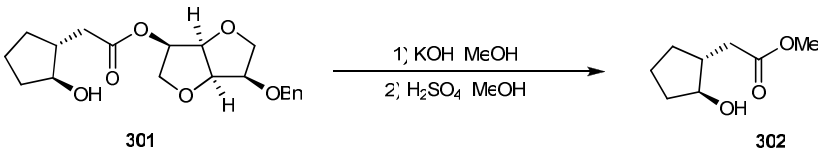
Disappointingly, the phenyl substituted substrate **296** did not cyclise under the reaction conditions and only unidentified non-cyclised products were obtained. In contrast, **297** was successfully cyclised to provide 'fused' ring product **299** in 54% yield and with a diastereoselectivity of 1:1. The only difference between the two substrates **296** and **297** is the activating group on the olefin, demonstrating that small differences can have important implications for reactivity in cyclisation reactions.

In 2003, Enholm and co-workers reported an extension to their earlier *O*-stannyl ketyl radical work by using isosorbide sugars as chiral auxiliaries to improve diastereoselectivity in aldehyde-alkene cyclisations (Eq 41).[84]



(41)

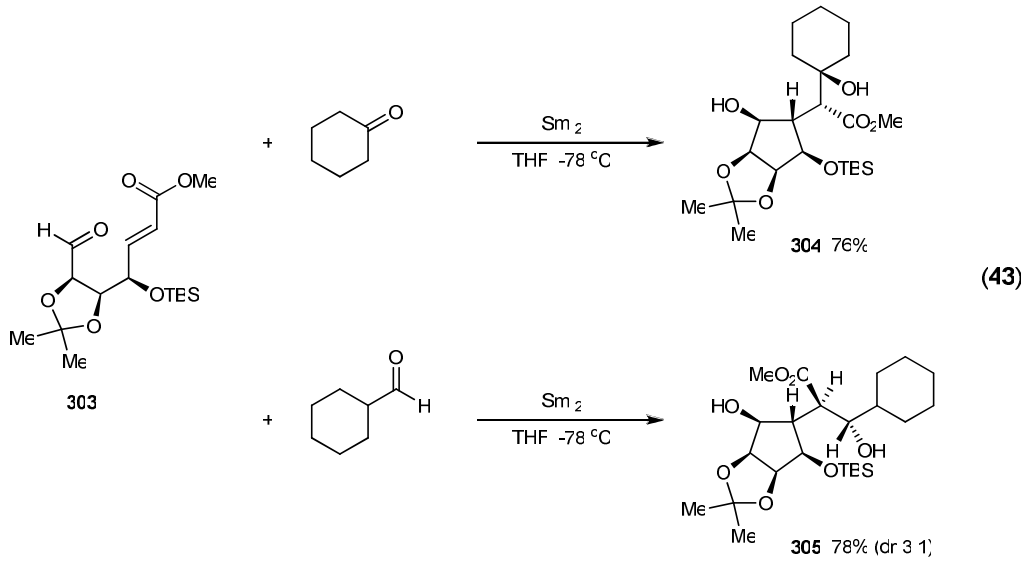
The isosorbide auxiliary can be easily removed and the product esterified as shown in Eq 42.



(42)

4.2.6 Samarium Iodide-Mediated Radical Reactions

In 1994, Enholm and co-workers disclosed a samarium diiodide-promoted formal homoaldol, *inter*molecular radical cyclisation.[85] In the key step, SmI_2 promotes a sequential one-electron cyclisation of an aldehyde carbonyl and an alkene, followed by a two-electron intermolecular carbonyl addition reaction (Eq 43).



(43)

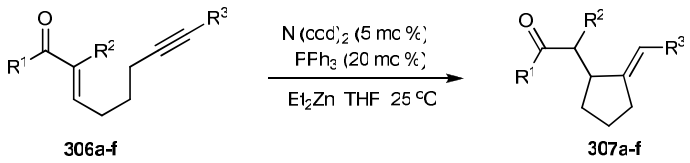
The bicyclic compound **304** was isolated as the sole observable stereoisomer. This is a remarkable result considering there are eight possible stereoisomeric products. The

isolation of **305** is more remarkable still. Given the potential for to up to sixteen possible stereochemical permutations in the four new stereocenters produced, the fact that only two diastereomers were obtained demonstrates the powerful selectivity of the reaction.

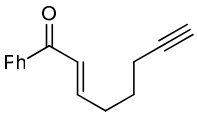
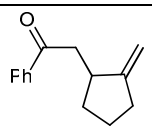
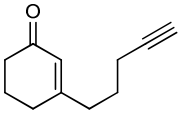
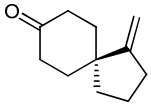
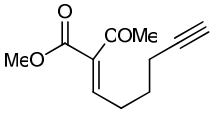
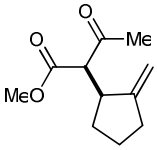
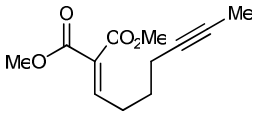
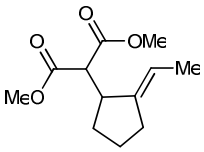
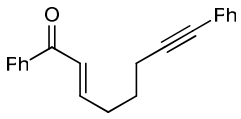
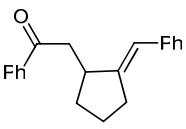
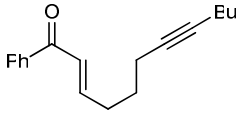
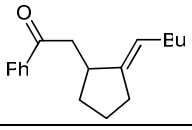
4.2.7 Nickel-Catalysed Cyclisations

In 1997 Montgomery and co-workers described the cyclisation of electron-deficient alkenes with tethered unsaturation, using a substoichiometric amount of $Ni(cod)_2$ in the presence of Et_2Zn (Table 39).[86]

Table 39: Nickel-Catalysed Cyclisation Reactions of Electron-Deficient Alkenes with Tethered Unsaturation

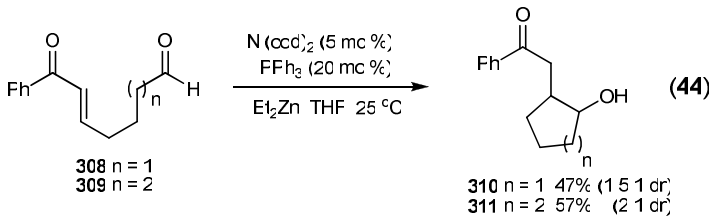


306a-f 307a-f

Entry	Alkyne		Product		Yield (%)
1		**306a**		**307a**	92
2		**306b**		**307b**	15
3		**306c**		**307c**	79
4		**306d**		**307d**	83
5		**306e**		**307e**	69
6		**306f**		**307f**	58

Cyclisations were generally achieved in good yield under mild conditions. The reaction tolerates substitution of the α,β-unsaturated carbonyl (entries 1 and 3) although the sterically demanding substrate **306b** (entry 2) leading to spirocyclisation proved to be much less efficient. Substitution of the alkyne with aliphatic (entries 4 and 6) and aromatic (entry 5) was also possible providing the desired product in good to excellent yields.

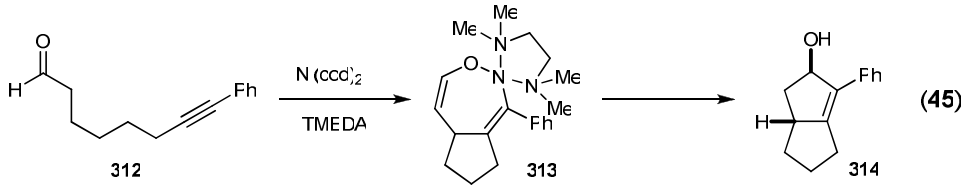
Significantly, aldoenones were also cyclised to provide formal homoaldol products (Eq 44).



(44)

Both five- and six-membered rings (**310** and **311** respectively) could be formed in moderate yield and with poor diastereoselectivity.

The closest precedent to the chemistry that will be discussed in chapter five was reported by Montgomery and co-workers in 2003.[87] By subjecting substrate **312** to $Ni(cod)_2$ with the ligand TMEDA, it was possible to obtain and isolate nickel enolate **313**. Subsequent quenching with MeOH produced the bicyclic species **314** (Eq 45).

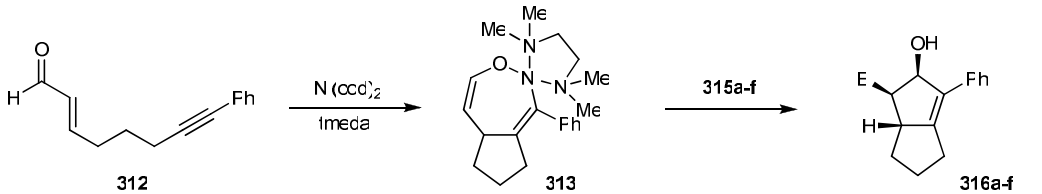


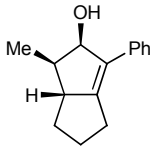
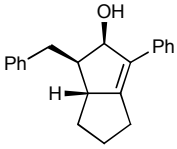
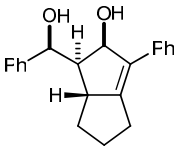
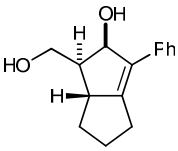
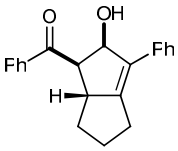
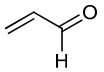
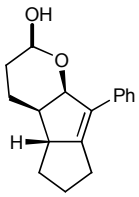
(45)

Montgomery reasoned that the reactive potential of **313** extended far beyond simple quenching. Exposure of this enolate to various electrophiles could lead to more valuable products with more new carbon-carbon bonds and stereocentres, all in one

pot. Subsequent tests with various electrophiles bore out this hypothesis and highlights are presented in Table 40.

Table 40: Nickel-Catalysed Tandem Cyclisations with Enolate Alkylation



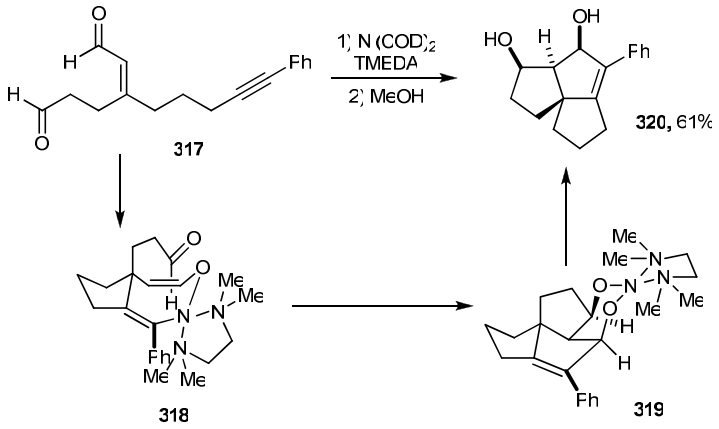
Entry	Electrophile (E^+)		Product		Yield (%)
1	CH_3	**315a**		**316a**	68
2		**315b**		**316b**	68
3		**315c**		**316c**	82
4	CH_2O	**315d**		**316d**	80
5		**315e**		**316e**	72
6		**315f**		**316f**	72[a]

a) Mixture of two diastereomers in ratio 1:1

Upon in situ generation of nickel enolate **313** followed by treatment with electrophiles **315a-f**, functionalised bicyclooctenols **316a-f** were obtained. Alkylations with methyl iodide (entry 1) and benzyl iodide (entry 2) provided single diastereomers of the bicyclooctenols that bear three contiguous stereocentres. Aldol

reactions were even more efficient, generating the desired products in 82% yield with benzaldehyde (entry 3) and 80% yield with formaldehyde (entry 4), both as single diastereomers and with four contiguous stereocentres. Nickel enolate **313** also undergoes efficient acylations to generate β-hydroxy ketone **316e** (entry 5) and even a Michael reaction with acrolein to generate tricyclic lactol **316f** as a mixture of two diastereomers (entry 6).

Encouraged by the generality and scope of the enolate alkylations within a metallacylic framework, the more elaborate dialdehyde **317** was prepared and treated with $Ni(cod)_2$/TMEDA followed by a methanol workup (Scheme 30).



Scheme 30: Reaction Pathway for Formation of Aldol Product 320

Dialdehyde **317** was successfully cyclised to provide the desired product **320** as a single diastereomer in 61% yield. Chemoselective oxidative cyclisation affords metallacycle **318**, followed by intramolecular aldol addition to afford nickel bis-alkoxide **319** which produces **320** upon workup with methanol. This reaction demonstrates the power of intramolecular cascade reactions. From a relatively simple acyclic substrate **317**, a complex polycyclic molecule has been created with the formation of two new carbon-carbon bonds, and quaternary carbon as part of four contiguous stereocentres, and all in one step. The drawback of this example is the reactions have to be performed with a stoichiometric quantity of $Ni(cod)_2$ which obviously limits the utility of the reaction.

4.3 Conclusions

There are many ways of obtaining formal homoaldol products. In some of these reactions, for example in the case of tin hydride and SmI_2, polycyclic products have been obtained from cascade reactions. Although these products are formed via a radical mechanism, they nevertheless demonstrate the potential of polycyclisation reactions in the formation of highly complex molecules from simple starting substrates.

The power of polycyclic cascade reactions has also been demonstrated by Montgomery using $Ni(cod)_2$ and Et_2Zn with systems bearing a far greater resemblance to the proposed methodology presented at the beginning of this chapter. Using simple linear acyclic starting substrates, nickel enolates are used to trap electrophiles, generating complex polycyclic products.

With these precedents in mind, we decided to embark on a programme of research that would seek to develop novel transition-metal-catalysed reductive homoaldol-initiated cascade reactions. This methodology has the potential to provide densely functionalised fused polycycles from relatively simple precursors just as modern organic chemistry seeks to develop methodologies that achieve rapid molecular complexity from simple achiral substrates.

4.4 References

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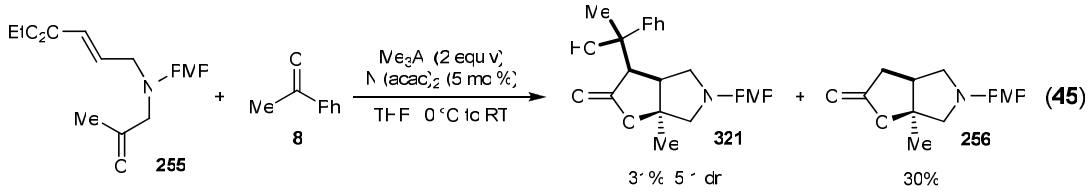
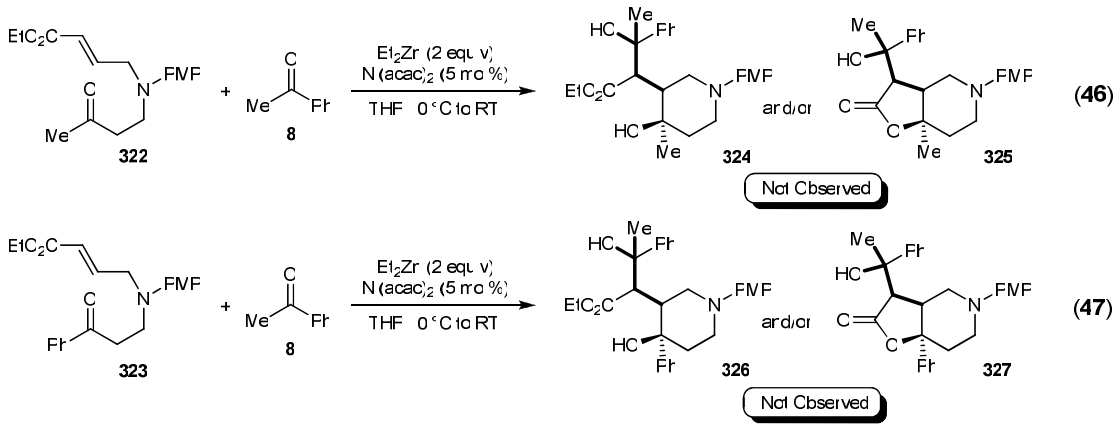
5 Nickel-Catalysed Formal Reductive Homoaldol-Initiated Cascade Reactions

In order to demonstrate the viability of trapping a zinc enolate with an electrophile as postulated in Eq 35 on page 125, α,β-unsaturated ester **255**[i] was subjected to the previous $Ni(acac)_2$ reaction conditions (see Eq 34, page 123) except that acetophenone (1.1 equiv) as an electrophile was also present. Although the reaction was successful with diethylzinc, there were fewer unidentified products when trimethylaluminium was used (Eq 45).



The reaction provided bicylic lactone **321** in 31% yield as a 5:1 inseparable mixture of diastereomers, along with a bicyclic side product **256** that had not incorporated acetophenone (**8**) in 30% yield. The relative stereochemistries of the isomers of **321** were not determined. This proof-of-concept reaction demonstrated the viability of trapping the zinc enolate resulting from homoaldol cyclisation with an electrophile in an intermolecular reaction, as had been postulated in Eq 35. Substrates **322** and **323** were prepared with the aim of producing six-membered lactams. These substrates were reacted under similar reaction conditions to **255** using both diethylzinc or trimethylaluminium (Eq 46 and Eq 47).

[i] Substrate **255** prepared by Euan. A. F. Fordyce

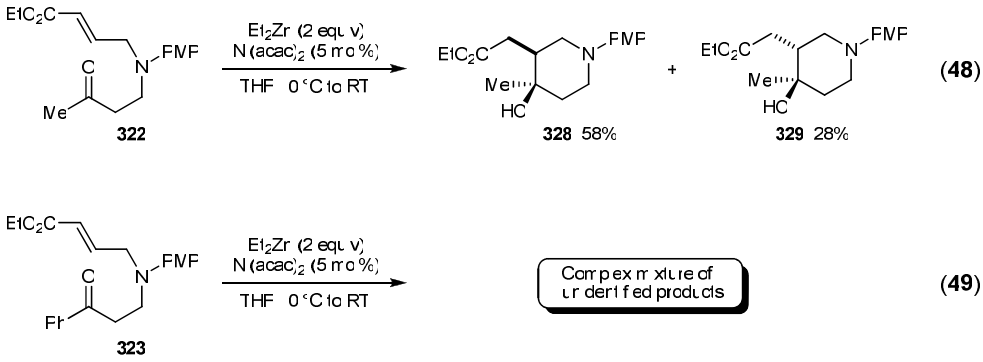


(46)

(47)

Unfortunately, neither of the desired six-membered lactams **324** or **326** or their lactonised derivatives **325** or **327** were observed, with only a complex mixture of unidentified products being obtained in both reactions.

However, when the reaction was repeated with **322** without acetophenone (**8**) present, clean cyclisation provided the desired lactam product with a diastereoselectivity of 7:3, the major diastereomer **328** being isolated in 58% yield, along with 28% of the minor diastereomer **329** (Eq 48). The attempted cyclisation of **323** without the presence of acetophenone (**8**) again resulted in only a complex mixture of unidentified products (Eq 49).

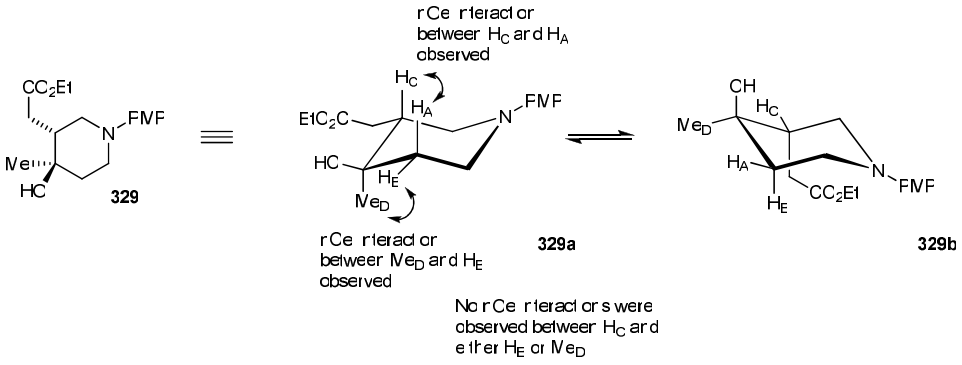


(48)

(49)

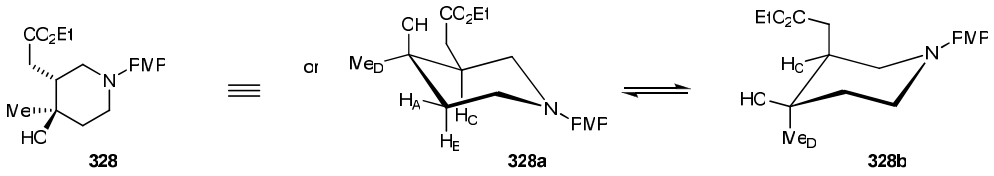
Experiments were performed to determine the relative stereochemistries of **328** and **329**. The chemical shifts of the protons H_A, H_B and H_C in the ^1H NMR spectrum of **329** were identified using HSQC ^1H NMR spectroscopy. Using 1D nOe ^1H NMR spectroscopy, these individual protons, along with those of the methyl group Me_D, were independently irradiated and the nOe interactions (or lack thereof) between

different protons were observed. It is likely that the minor diastereomer **329** adopts a chair in preference to a boat conformation, and the two most probable conformations are illustrated in Scheme 31.



Scheme 31: Two Possible Conformations of Minor Diastereomer 329

It is unlikely the minor diastereomer adopts confirmation **329b**, as this involves the ester group residing in a highly disfavoured axial position. The expected nOe interactions present in structure **329a**, between H_C and H_A and between H_B and Me_D are observed supporting the conclusion that the relative stereochemistry of the minor diastereomer **329** is **329a**. Although it was not possible to conduct 1D nOe ^{1}H NMR spectroscopic experiments with the major diastereomer **328** due to many overlapping signals on the ^{1}H NMR spectrum, an assignment may be made based on a process of elimination. The two most probable chair conformations of the major diastereomer are illustrated in Scheme 32.

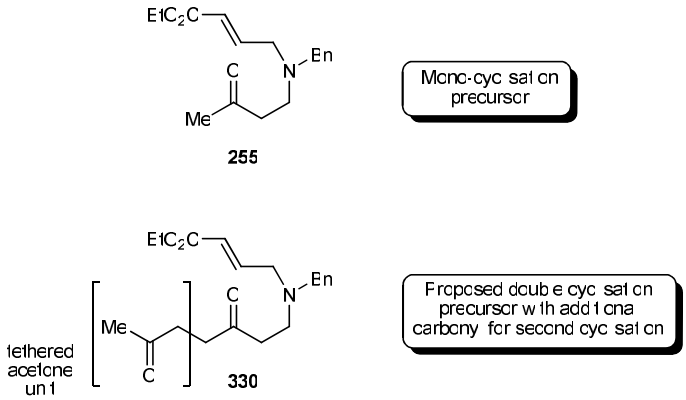


Scheme 32: Two Possible Conformations of Major Diastereomer

It is unlikely the conformation of the major diastereomer is **328b** as this would involve the ester group adopting a highly disfavoured axial position. Therefore the major diastereomer is tentatively assigned as conformation **328a** in Scheme 32.

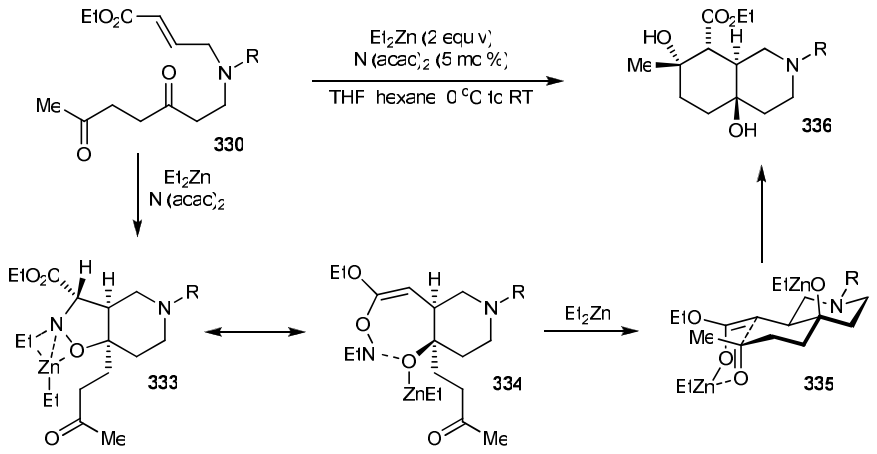
The results of Eq's 48, and 45 demonstrate that both five- and six-membered lactams can be synthesised via the nickel-catalysed formal reductive homoaldol reaction. In addition, it has been demonstrated that zinc or aluminium enolates (postulated in the mechanism shown in scheme 27), generated after the formation of a five-membered ring can be trapped by an electrophile (Eq 45). The limitation of this methodology occurs when a six-membered ring is formed prior to the generation of a possible enolate. In these cases, there has been little evidence to suggest that an electrophile can trap a metal enolate in an intermolecular reaction. This lack of evidence may be down to poor diastereoselectivity resulting in the formation of lots of different products in low yield. However, the cyclisation of substrates to form five- or six-membered rings that possess an extra tethered ketone may have inherent geometric constraints. These constraints may allow both the trapping of an electrophile and the generation of very high diastereoselectivity in the second cyclisation. If this is the case, it is not unreasonable to expect the overall diastereoselectivity of a possible double cyclisation product to be higher than the current monocyclised products. For this reason, reactions that form an initial five-membered ring or an initial six-membered ring will be attempted.

In order to attempt the proposed double cyclisation reactions it was first necessary to prepare the required precursor substrates. These substrates are similar to the monocyclisation precursors **255** except that they have an extra electrophilic component tethered to the molecule by a hydrocarbon chain. This is illustrated in Scheme 33.



Scheme 33: Proposed Double Cyclisation Precursor

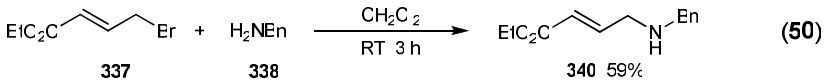
On exposure of **330** to the standard nickel-diethyl-zinc conditions, the expected reaction pathway would proceed as illustrated in Scheme 34 below.

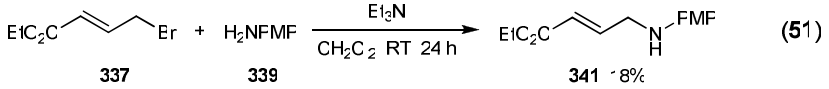


Scheme 34: Proposed Reaction Pathway of 330 in Nickel-Catalysed Reductive Homoaldol Reaction

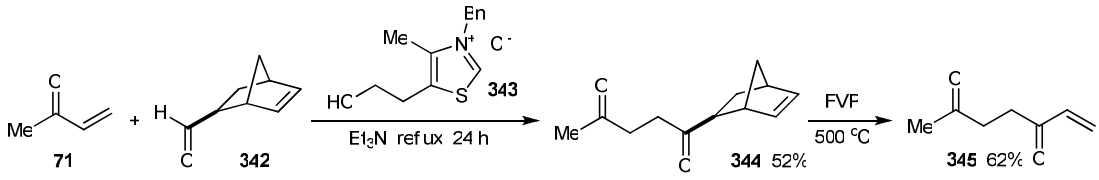
Initial coordination to **330** with Ni(0) at the alkene of the α,β-unsaturated ester followed by oxidative cyclisation with the proximal ketone, should lead to oxanickellacycle **333**. This would likely form the more favoured cis-fused ring junction as opposed to the likely higher energy fused ring junction. Transmetallation followed by rapid tautomerisation to the *Z*-*O*-bound enolate forms **334**, which after a further transmetallation with Et_2Zn will provide *Z*-zinc enolate **335**. This enolate, via a Zimmerman-Traxler-type transition state,[88] should then provide the desired bicycle **336** with the stereochemistry shown.

Initially, two cyclisation precursors (**330** and **331**) were prepared, differing only in whether the nitrogen was protected by a benzyl group or with a *p*-methoxyphenyl group. First, the two secondary amines **340** and **341** were prepared from benzylamine and *p*-anisidine respectively (Eq 50 and Eq 51).



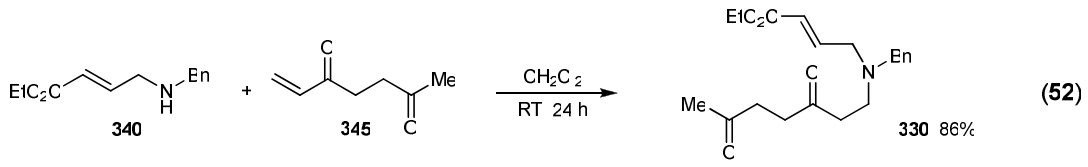


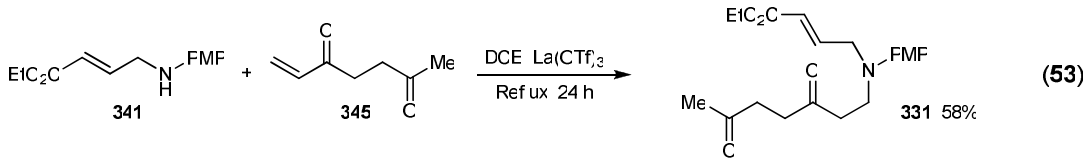
Next, the enone **345** was prepared from a Stetter reaction of methyl vinyl ketone (**72**) with **342**,[89] followed by retro-Diels-Alder extrusion of cyclopentadiene from **344** by flash vacuum pyrolysis (Scheme 35).



Scheme 35: Preparation of Dicarbonyl 345

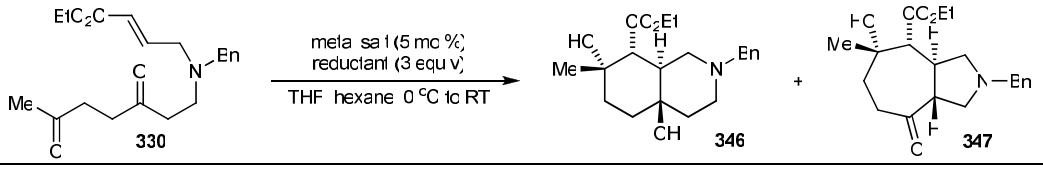
Conjugate addition of the amines **340** and **341** to enone **345** resulted in the formation of the desired cyclisation precursors **330** and **331** respectively (Eq 52 and 53).





The cyclisation precursor **330** was now subjected to a range of cyclisation conditions (Table 41).

Table 41: Cyclisation Reactions of 330 Varying the Catalyst and Stoichiometric Reductant



Entry	Metal Salt	Reductant	Observations[a]
1	$Ni(acac)_2$	Et_2Zn	Mixture of many unidentified products
2	$Ni(acac)_2$	Et_3Al	Mixture of many unidentified products
3	$(PPh_3)_2NiBr_2$	Et_2Zn	Mainly **330** recovered
4	$(PCy_3)_2NiBr_2$	Et_2Zn	Mainly **330** recovered
5	$Co(acac)_2{\cdot}2H_2O$	Et_2Zn	Mixture of many unidentified products
6	$Co(acac)_2{\cdot}2H_2O$	Et_3Al	Mixture of many unidentified products
7	$(Me_3P)_2NiCl_2$	Et_3Al	Mixture of many unidentified products
8	$(Me_3P)_2NiCl_2$	Et_2Zn	**347** isolated in 15% yield

a) All reactions run for 24 h at room temperature. Unless noted, **330** was consumed in the reaction.

Exposure of **330** to the standard reaction conditions (entry 1) resulted in only an intractable mixture of unidentified products. The same observation was made when triethylaluminium was used in place of diethylzinc (entry 2). The use of $(PPh_3)_2NiBr_2$ (entry 3) and $(PCy_3)_2NiBr_2$ (entry 4), catalysts which both possess bulky ligands, resulted in the recovery of almost exclusive starting material. $Co(acac)_2{\cdot}2H_2O$ was used with both diethylzinc and triethylaluminium but only an intractable mixture of unidentified products was observed (entries 5 and 6). The use of $(Me_3P)_2NiCl_2$ as a catalyst in combination with triethylaluminium also provided only an intractable mixture of unidentified products (entry 7). However, when diethylzinc was used in combination with $(Me_3P)_2NiCl_2$, the unexpected bicyclic product **347** was isolated in 15% yield (entry 3) and an X-ray crystal structure was obtained (Figure 10). The remaining 85% consisted of a complex mixture of inseparable, unidentified products.

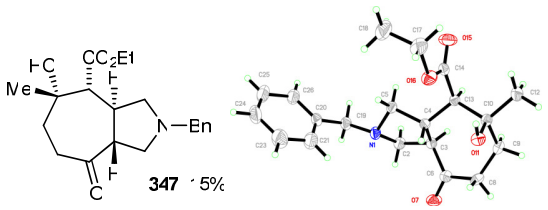
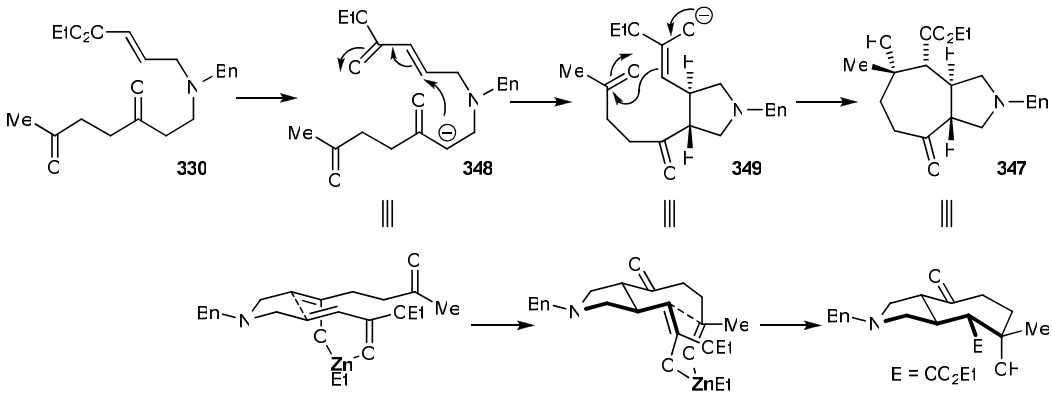


Figure 10: Structure of 347

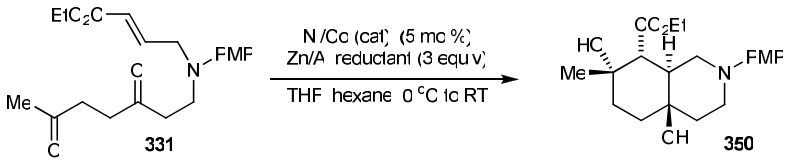
It is likely that **347** is formed by the following mechanism (Scheme 36).



Scheme 36: Proposed Mechanism to Account for Formation of 347

Deprotonation of **330** forms **348**, which allows Michael addition to the β-carbon of the alkene, forming a five-membered ring and generating enolate **349**. An aldol reaction of this enolate onto the pendant carbonyl followed by protonation on workup results in the bicyclic product **347**. Interestingly, the formation of **347** requires the presence of both a stoichiometric quantity of Et_2Zn and at least a catalytic amount of $Ni(acac)_2$. Although the original planned reaction pathway involving enolates to cyclise **330** to **346** had failed, an interesting and potentially as valuable side product **347** had formed instead. Investigation into this new system will be described later in this chapter.

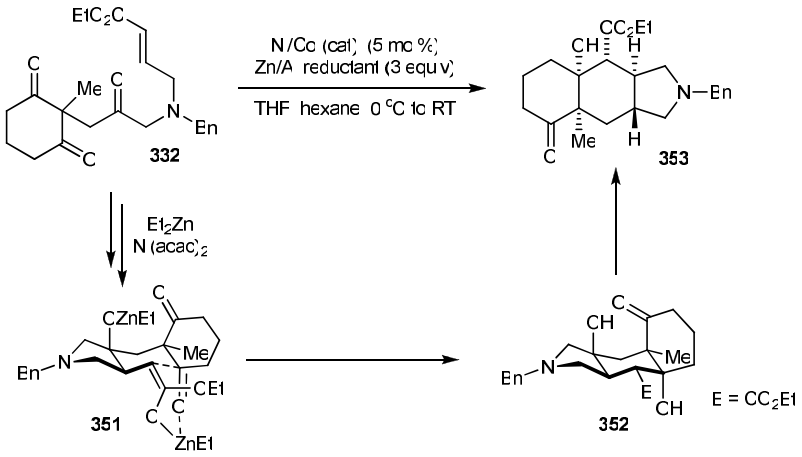
The desired nickel-catalysed reductive homoaldol cyclisation of benzyl protected **330** had been unsuccessful and so attention was turned to attempting the desired cyclisation with the *p*-methoxyphenyl protected substrate **331** (Eq 54).



(54)

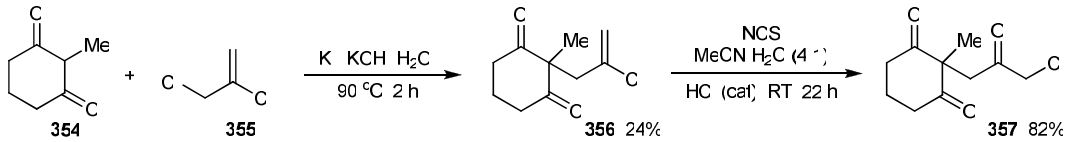
Reactions were attempted with $Ni(acac)_2$, $(Me_3P)_2$ $NiCl_2$, and $Co(acac)_2 \cdot 2H_2O$ with both diethylzinc and triethylaluminium. In all the reactions, although **331** was consumed in the reaction, the reactions always provided an inseparable mixture of multiple unidentified products.

Reactions with cyclisation precursors **330** (benzyl) and **331** (PMP) that initially form a six-membered ring in a formal reductive homoaldol step had been unsuccessful in that the desired products **346** and **350** had not been obtained. However, during the earlier monocyclisation studies not only had five-membered rings been successfully synthesised, but the enolate resulting from the cyclisation (Eq 45) was successfully trapped by acetophenone. For these reasons, attention was now turned to attempting the double cyclisation with a precursor that would form a five-membered ring in the initial formal reductive homoaldol cyclisation. The complexity of the proposed triple fused ring product makes the stereochemistry more difficult to predict. A tentative reaction pathway is presented in Scheme 37.



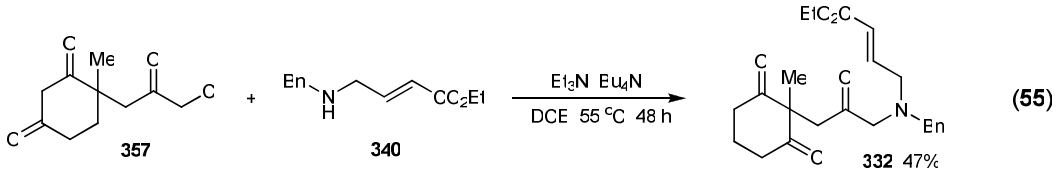
Scheme 37: Proposed Reaction Pathway to Account for Formation of 353

In order to attempt the reaction that provides **353** it was first necessary to prepare the cyclisation precursor **332**. Addition of 2-methyl-1,3-cyclohexadiene (**354**) to allyl chloride **355** provided monochloro substrate **356**,[90] which on treatment with NCS in MeCN:H_2O (4:1) gave α-chloroketone **357** (Scheme 38).[91]

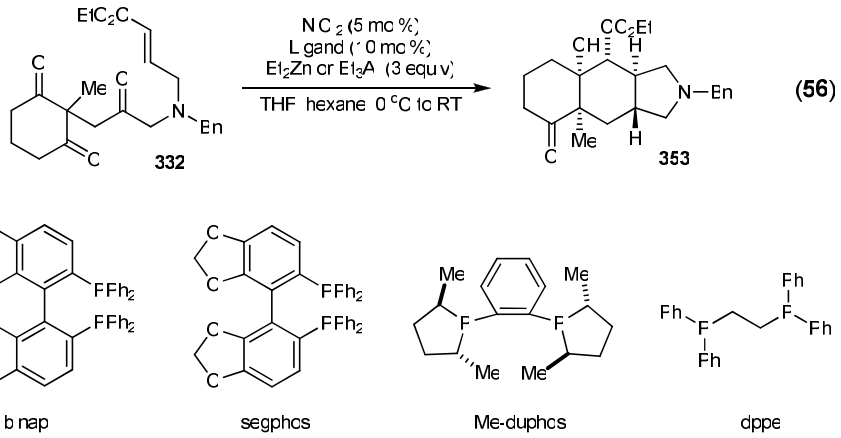


Scheme 38: Preparation of α-chloroketone 357

Alkylation of the allylamine **340** with monochloro **357** provided **332** in 47% yield (Eq 55).

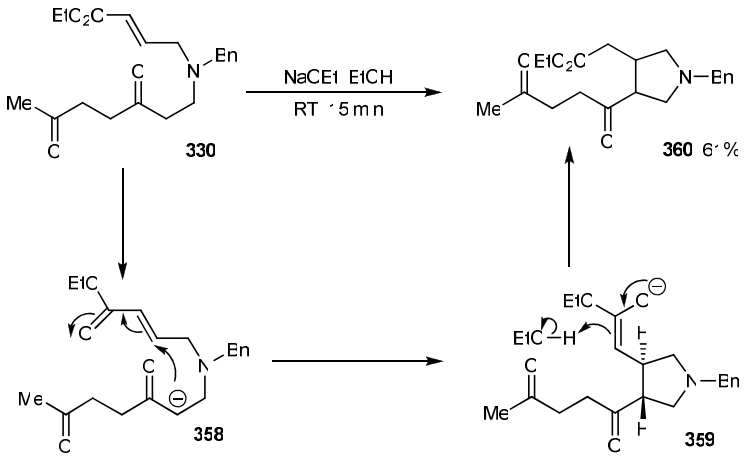


The cyclisation precursor **332** was exposed to a range of conditions similar to those used on **330**. Reactions performed with the catalysts $Ni(acac)_2$ or $(Me_3P)_2NiCl_2$ or $Co(acac)_2{\cdot}2H_2O$ in combination with one of the reductants diethylzinc or triethylaluminium resulted in the formation of multiple inseparable unidentified products. When the bulkier catalyst $(PPh_3)_2NiBr_2$ was used, only starting material was recovered. Although in most of the reactions, the cyclisation precursor **332** was being consumed, a lack of selectivity was resulting in the formation of multiple products. In an attempt to improve the selectivity of the reaction, the ligands binap, segphos, duphos, and dppe were used in combination with $NiCl_2$ as catalyst and either diethylzinc or triethylaluminium (Eq 56).



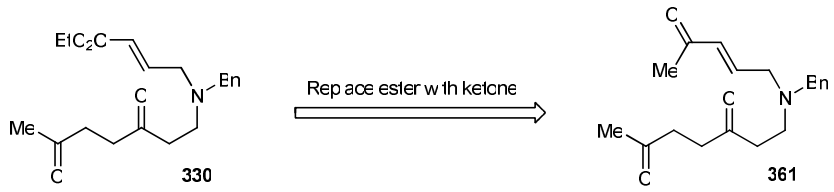
In the event, the ligands appeared to decrease the rate of reaction so that in all cases, mostly starting material was recovered. In some cases a mixture of inseparable unidentified products was also obtained.

The desired nickel-catalysed formal homoaldol cyclisations had been unsuccessful, but in the course of work with the cyclisation precursor **330** another bicyclic product **347** had been isolated (Table 41). This fused seven-five ring product had not been expected. However since two new rings and four contiguous stereocentres had been created in one reaction it warranted further investigation. This new reaction appeared to rely on deprotonation, after which spontaneous cyclisation can occur. Based on this assumption, a new reaction was performed with **330** (Scheme 39).



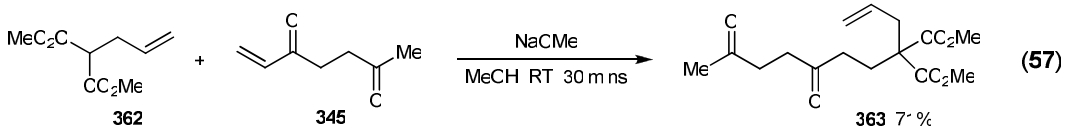
Scheme 39: Proposed Mechanism for Formation of 360

Treatment of **330** with NaOEt provided the monocyclised product **360,** isolated in 61% yield as a single diastereomer although it was not possible to assign the relative stereochemistry of this molecule. The second cyclisation was not observed but this is perhaps not surprising given that the reaction was performed in a protic solvent, under reversible conditions, and the reaction was quenched after 15 minutes. The strength of NaOEt as a base means an overall preferential deprotonation of ketones over the ester is the likely result. In order to increase the chances of deprotonation of the ester after the first cyclisation had completed, the ester functional group was changed to another ketone as illustrated in Scheme 40.



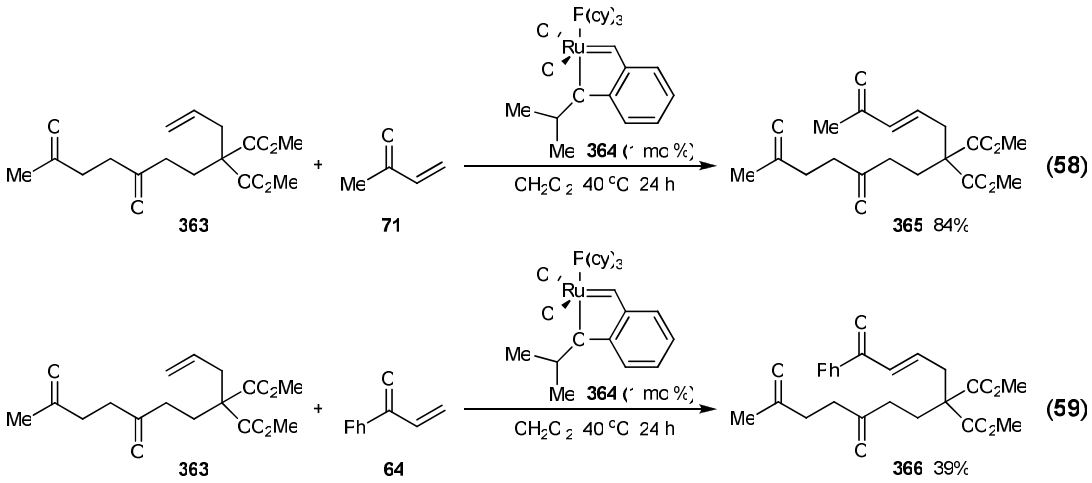
Scheme 40: Substrate Modification Incorporating an Enone in Place of an α,β-Unsaturated Ester

Two modified substrates were prepared that have enones instead of α,β-unsaturated esters. Starting from the commercially available dimethyl molanate derived precursor **362**, Michael addition to **345** provided **363** in 71% yield (Eq 57).



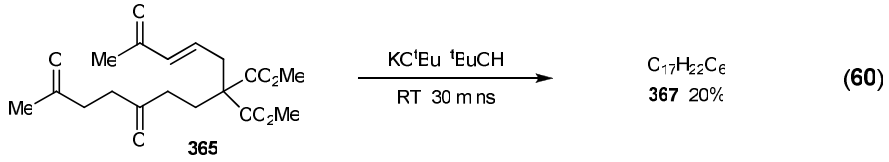
(57)

The olefin **363** was then functionalised using Hoveyda-Grubbs 1st generation catalyst (**364**) in a cross alkene metathesis with either methyl vinyl ketone (**71**) or phenyl vinyl ketone (**64**) (Eq's 58 and 59).

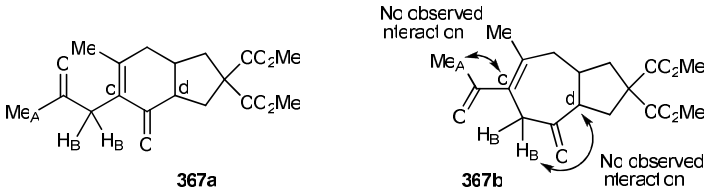


These metathesis reactions successfully provided the desired cyclisation precursors **365** and **366** in 84% and 39% yield respectively.

Cyclisation precursor **365** was now subjected to a range of cyclisation conditions including KO^{t}Bu in *t*-BuOH, K_2CO_3 in *t*-BuOH and NaOMe in MeOH. Reactions with K_2CO_3 resulted in only the recovery of the starting cyclisation precursor while the use of NaOMe provided a complex mixture of unidentified products. However, the use of KO^{t}Bu in *t*-BuOH provided **367** which from mass spectroscopic analysis has the formula $C_{17}H_{22}O_6$ and was isolated in 20% yield (Eq 60).



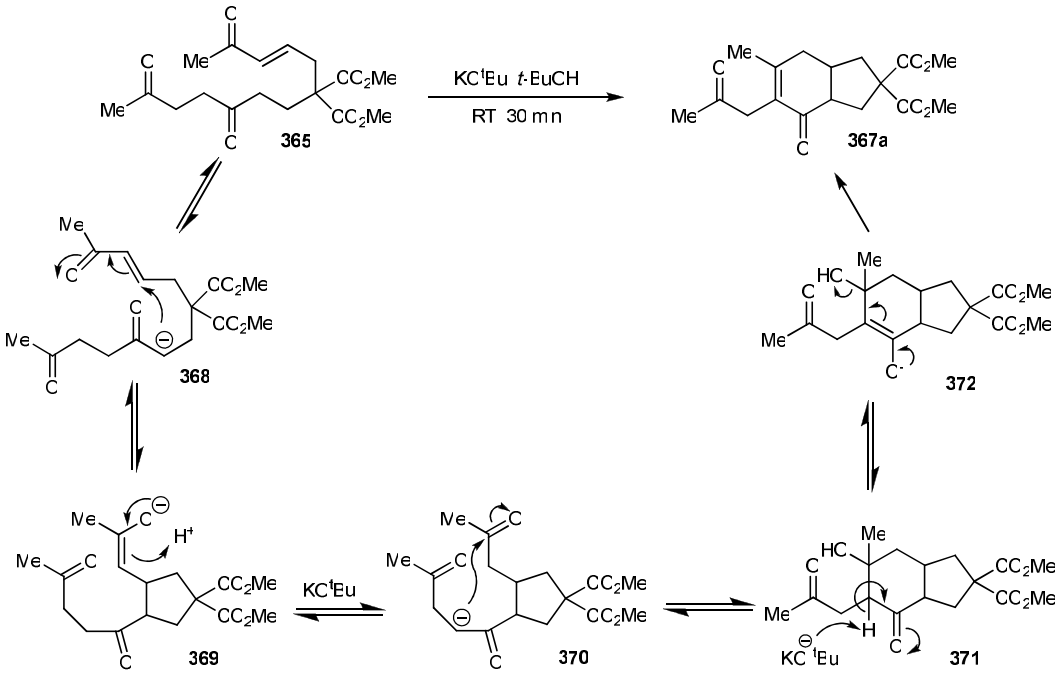
As well as mass spectroscopy, analysis of **367** by ^{1}H and ^{13}C NMR spectroscopy narrowed the structure of **367** to two likely candidates illustrated in Scheme 41.



Scheme 41: Two Possible Structures for 367

HMBC NMR experiments were performed to identify the correct structure. If the structure were **367b**, then an HMBC interaction between carbon C and the protons on the methyl group (Me_A) would be expected but this is not observed. In addition, if **367b** were the correct structure then carbon D would interact with the protons H_B but this too is not observed. The lack of evidence to support **367b** as the structure leads to the tentative assignment of **367a** as the correct structure.

Although **365** successfully completed a double cyclisation, the resultant hydroxy group then underwent E1cB elimination, destroying two stereocentres. A possible reaction pathway for the formation of **367a** is presented in Scheme 42.

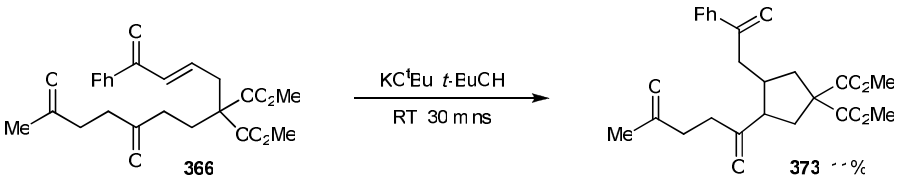


Scheme 42: Postulated Mechanism for Formation of 367a

Deprotonation of **365** induces the first cyclisation, forming the enolate **369** and creating the first ring. A second deprotonation of monocycle **370** leads to the formation of the fused ring product **371**. Deprotonation at this different ketone may be because the resultant cyclisation leads to the formation of a six-membered ring (**371**). Cyclisation of **369** would form a seven-membered ring but cyclisation to form a six-membered ring may be faster and so the bicyclic product **371** is formed

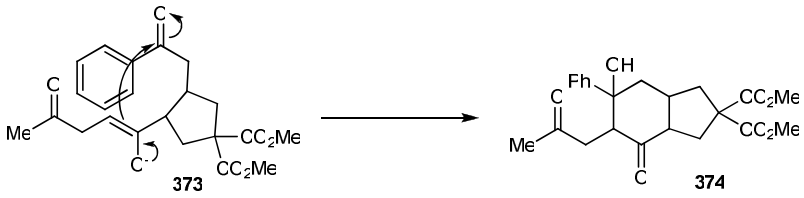
preferentially. Finally, the newly created tertiary alcohol from **371** undergoes E1cB elimination to provide enone **367a**.

Using the same conditions that were used to cyclise **365** (Eq 60), the phenyl substituted cyclisation precursor **366** was subjected to KO^{t}Bu in *t*-BuOH, (Eq 61).



(61)

In this case, only the first cyclisation completed, resulting in the isolation of **373** in 11% yield. The relative stereochemistry was not assigned. A possible reason for the formation of only the monocyclised product is illustrated in Scheme 43.



Scheme 43: Bulky Phenyl Group Blocking Second Cyclisation to Form 374

It is possible that the more bulky phenyl group present in **366** prevents a second cyclisation from completing after an initial deprotonation. In addition, the reaction was only performed for 30 minutes. If the reaction had been run for longer, perhaps 24 hours, then the second cyclisation may have had time to complete.

5.1 Conclusions

Based on earlier results obtained by our group, the possibility of a nickel-catalysed formal reductive homoaldol-initiated cascade reaction was investigated. Formal homoaldol cyclisations generated an enolate, and the viability of trapping this enolate with an external electrophile was first explored. This work was successful in that cyclisations provided five-membered rings and the enolate generated from the cyclisation was successfully trapped by acetophenone. Efforts to repeat this success with substrates that cyclise to form six-membered rings were less successful. Although substrates that cyclised to form six-membered rings could be cyclised on their own, the aim of incorporating an external electrophile was not achieved. Despite these limitations, the feasibility of trapping an electrophile with an enolate formed as the result of a cyclisation was demonstrated.

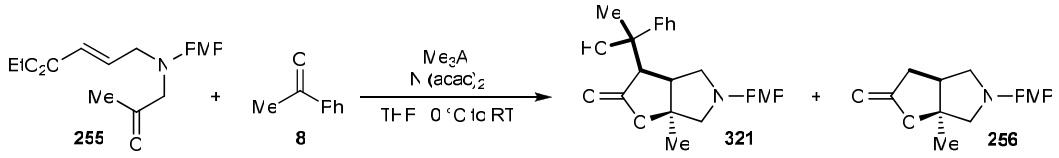
Attempts to build on this success by developing nickel-catalysed double cyclisation reactions were less successful as it could not be confirmed that any of the desired products had been obtained. It is possible that the cyclisation precursors are just too dissimilar from their simpler, monocyclic equivalents and so the assumed comparisons between the too were unrealistic. This reasoning is supported by the unexpected isolation of the fused seven-five-membered ring product, formed from a completely different reaction pathway from the one envisioned. Attempts to explore and develop this methodology were only partially successful. The main problem was lack of selectivity since different substrates reacted in different ways to provide different product types under the same reaction conditions. This lack of control over the reaction pathway was confounded by very poor yields.

Despite these poor results, there remains much potential in both the nickel-catalysed cascade and the base-catalysed cascade work. Both methods are atom economical and the base-catalysed reaction in particular uses very mild conditions and provides a doubly fused ring with four contiguous stereocentres from an achiral precursor in 15% yield. Development of the base-catalysed methodology based on further

substrate modification and methodology screening may lead to both improved yields and greater control of the reactions.

5.2 Experimental

(3a*S*,6a*S*)-3-(1-Hydroxy-1-phenyl-ethyl)-5-(4-methoxy-phenyl)-6a-methyl hexahydro-furo[2,3-*c*]pyrrol-2-one (321) and (3a*S*,6a*S*)-5-(4-Methoxy-phenyl)-6a-methyl-hexahydro-furo[2,3-*c*]pyrrol-2-one (256)



A solution of **255**[i] (100 mg, 0.34 mmol), acetophenone (**8**) (44 μL, 1.10 mmol) and $Ni(acac)_2$ (8.8 mg, 0.034 mmol), in THF (4.0 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_3Al (1 M solution in hexane, 0.69 mL, 0.69 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 4 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (10 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the aldol product **321** as an inseparable mixture of diastereomers in the ration 5:1 (44 mg, 31%) as a colourless oil followed by the aldol product **256** (30 mg, 22%) as a colourless oil.

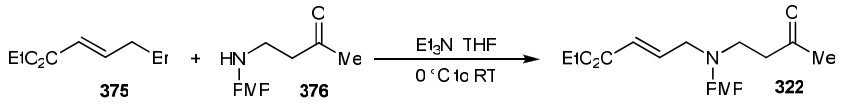
Data for **321** (Major diastereomer): IR (film) 3463 (OH), 2930, 2833, 1746 (C=O), 1513, 1244, 1173, 1038, 978, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57-7.32 (5H, m, Ar**H**), 6.79 (2H, d, *J* = 9.1, Hz, Ar**H**), 6.52 (2H, d, *J* = 9.1, Hz, Ar**H**), 3.75 (3H, s, C**H**$_3$O), 3.06-3.01 (2H, m, OCC**H**$_2$N), 2.81-2.74 (3H, m, CHC**H**$_2$N and O=CC**H**CH), 2.47-2.43 (1H, m, O=CCHC**H**), 1.81 (3H, s, CHCC**H**$_3$), 1.31 (3H, s, HOCC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.0 (C), 153.0 (C), 143.7 (C), 142.3 (C), 128.5 (2 x CH), 127.8 (CH), 125.6 (2 x CH), 115.7 (2 x CH), 114.7 (2 x CH), 89.7 (C), 74.6 (C), 61.8 (CH_2), 60.5 (CH), 55.9 (CH_2), 55.6 (CH_3), 53.4 (CH), 47.3

[i] Substrate **255** prepared by Euan. A. F. Fordyce

(CH_3), 24.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{25}NO_4$ $[M+H]^+$: 368.1856, found: 368.1856. Diagnostic peaks for **321** (Minor diastereomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.91 (2H, m, Ar**H**), 6.85-6.83 (2H, m, Ar**H**), 6.59-6.57 (2H, m, Ar**H**), 3.75 (3H, s, C**H**$_3$O), 1.90 (3H, s, CHCC**H**$_3$).

Data for **256**: IR (film) 2933, 2833, 1770 (C=O), 1515, 1244, 1178, 1037, 962, 819, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (2H, dm, *J* = 9.1 Hz, Ar**H**), 6.62, (2H, dm, *J* = 9.1 Hz, Ar**H**), 3.78 (1H, d, *J* = 10.8 Hz, C**H**$_2$N), 3.77 (3H, s, OC**H**$_3$), 3.40 (1H, dd, *J* = 9.7, 7.5 Hz, C**H**$_2$N), 3.31 (1H, dd, *J* = 9.7, 3.8 Hz, C**H**$_2$N), 3.10 (1H, d, *J* = 10.8 Hz, C**H**$_2$N), 2.98 (1H, dd, *J* = 18.1, 9.6 Hz, C**H**$_2$C=O), 2.85-2.80 (1H, m, C**H**CH$_2$N), 2.59 (1H, dd, *J* = 18.1, 3.3 Hz, C**H**$_2$C=O), 1.62 (3H, s, C**H**$_3$CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.7 (C), 152.6 (C), 142.2 (C), 115.0 (2 x CH), 114.8 (2 x CH), 91.8 (C), 60.9 (CH_2), 56.0 (CH_2), 55.7 (CH_3), 43.4 (CH), 35.9 (CH_2), 24.2 (CH_3); HRMS (EI) Exact mass calcd for $C_{14}H_{17}NO_3$ $[M]^+$: 247.1203, found: 247.1201.

(E)-4-[(4-Methoxy-phenyl)-(3-oxo-butyl)-amino]-but-2-enoic acid ethyl ester (322)

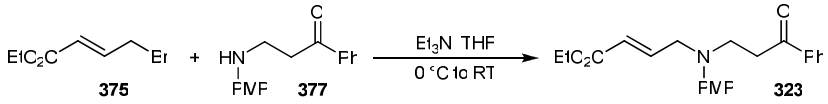


To a stirred solution of **376**[i] (1.00 g, 5.60 mmol), Et_3N (1.60 mL, 11.30 mmol), in THF (50 mL) at 0 °C was added ethyl-4-bromocrotonate (75% pure) (**375**) (2.03 mL, 11.30 mmol) dropwise over 5 min. The reaction was stirred at 0 °C for 30 min and then at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL), and then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and H_2O (30 mL) and then dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) afforded the tertiary amine **322** (1.157 g, 68%) as a brown oil. IR (film) 2983, 2905, 1714 (C=O), 1513, 1366, 1244, 1175, 1039, 816, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (1H, dt, *J* = 15.7, 4.6 Hz, CH=C**H**CH$_2$), 6.84-6.80 (2H, m, Ar**H**), 6.66-6.61 (2H, m, Ar**H**), 5.89 (1H, dt, *J*

[i] Substrate **376** prepared by Euan. A. F. Fordyce

= 15.7, 1.9 Hz, C**H**=CHCH$_2$), 4.17 (2H, q, *J* = 7.1 Hz, CH$_3$C**H**$_2$O), 4.00 (2H, d, *J* = 2.7 Hz, CHC**H**$_2$N), 3.76 (3H, s, OC**H**$_3$), 3.55 (2H, t, *J* = 6.9 Hz, NC**H**$_2$CH$_2$CO), 2.71 (2H, t, *J* = 6.9 Hz, NCH$_2$C**H**$_2$CO), 2.14 (3H, s, CH$_3$CO), 1.27 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 207.6 (C), 166.2 (C), 152.2 (C), 145.0 (CH), 141.7 (C), 122.1 (CH), 114.9 (4 x CH), 60.3 (CH$_2$), 55.7 (CH$_3$), 53.2 (CH$_2$), 46.3 (CH$_2$), 41.4 (CH$_2$), 30.5 (CH$_3$), 14.2 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{17}$H$_{24}$NO$_4$ [M+H]$^+$: 306.1700, found: 306.1703.

(E)-4-[(4-Methoxy-phenyl)-(3-oxo-3-phenyl-propyl)-amino]-but-2-enoic acid ethyl ester (323)

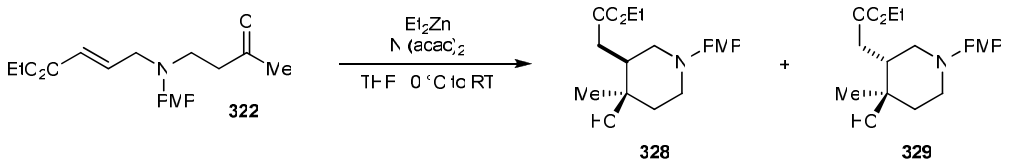


To a stirred solution of **377**[i] (1.00 g, 4.20 mmol), Et$_3$N (1.17 mL, 8.40 mmol), in THF (70 mL) at 0 °C was added ethyl-4-bromocrotonate (75% pure) (**375**) (1.50 mL, 8.40 mmol) dropwise over 5 min. The reaction was stirred at 0 °C for 30 min and then at room temperature for 22 h. The reaction was quenched with saturated aqueous NH$_4$Cl solution (30 mL), and then extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and H$_2$O (30 mL) and then dried (MgSO$_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) afforded the tertiary amine **323** (1.13 g, 77%) as an orange oil. IR (film) 2982, 2833, 1717 (C=O), 1680 (C=O), 1513, 1274, 1244, 1178, 1038, 815, 690 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94-7.91 (2H, m, Ar**H**), 7.59-7.54 (1H, m, Ar**H**), 7.48-7.43 (2H, m, Ar**H**), 6.96 (1H, dt, *J* = 15.7, 4.6 Hz, CH=C**H**CH$_2$), 6.86-6.82 (2H, m, Ar**H**), 6.70-6.66 (2H, m, Ar**H**), 5.93 (1H, dt, *J* = 15.7, 1.9 Hz, C**H**=CHCH$_2$), 4.17 (2H, q, *J* = 7.1 Hz, CH$_3$C**H**$_2$O), 4.06 (2H, dd, *J* = 4.6, 1.9 Hz, CHC**H**$_2$N), 3.76 (3H, s, OC**H**$_3$), 3.76 (2H, t, *J* = 7.0 Hz, NC**H**$_2$CH$_2$C=O), 3.26 (2H, t, *J* = 7.0 Hz, NCH$_2$C**H**$_2$C=O), 1.27 (3H, t, *J* = 7.1 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 199.1 (C), 166.2 (C), 152.1 (C), 145.0 (CH), 141.7 (C), 136.8 (C), 133.2 (CH), 128.6 (2 x CH), 128.0 (2 x CH), 122.1 (CH),

[i] Substrate **377** prepared by Euan. A. F. Fordyce

115.0 (2 x CH), 114.6 (2 x CH), 60.3 (CH_2), 55.7 (CH_3), 53.2 (CH_2), 47.0 (CH_2), 36.3 (CH_2), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{26}NO_4$ $[M+H]^+$: 368.1856, found: 368.1856.

[(3S,4R)-4-Hydroxy-1-(4-methoxy-phenyl)-4-methyl-piperidin-3-yl]-acetic acid ethyl ester (328) and [(3R,4R)-4-Hydroxy-1-(4-methoxy-phenyl)-4-methyl-piperidin-3-yl]-acetic acid ethyl ester (329)

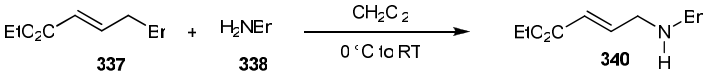


A solution of **322** (100 mg, 0.33 mmol), and $Ni(acac)_2$ (7.4 mg, 0.033 mmol), in THF (4.0 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.66 mL, 0.66 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 18 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (10 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the aldol product **328** (59 mg, 58%), as a colourless oil followed by the aldol product **329** (29 mg, 28%) as a colourless oil.

Data for **328**: IR (film) 3506 (OH), 2937, 2831, 1707 (C=O), 1514, 1468, 1242, 1178, 1039, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85-6.82 (2H, m, Ar**H**), 6.66-6.64 (2H, m, Ar**H**), 4.24-4.10 (2H, m, $CH_3C\mathbf{H}_2O$), 3.76 (3H, s, $C\mathbf{H}_3O$), 3.67-3.27 (4H, m, $COCH_2CHC\mathbf{H}_2N$ and $HOCCH_2C\mathbf{H}_2N$), 2.64-2.51 (2H, m, $COC\mathbf{H}_2CHCH_2N$), 1.95-1.90 (1H, app dd, J = 10.3, 3.8 Hz, $COCH_2C\mathbf{H}CH_2N$), 1.85-1.74 (2H, m, $HOCC\mathbf{H}_2CH_2N$), 1.27 (3H, t, J = 7.1 Hz, $C\mathbf{H}_3CH_2O$), 1.26 (3H, s, $C\mathbf{H}_3COH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.6 (C), 151.0 (C), 144.4 (C), 114.9 (2 x CH), 112.6 (2 x CH), 71.0 (C), 60.7 (CH_2), 55.9 (CH_3), 52.0 (CH), 48.0 (CH_2), 43.1 (CH_2), 42.5 (CH_2), 29.6 (CH_3), 25.7 (CH_2), 14.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{26}NO_4$ $[M+H]^+$: 308.1856, found: 308.1850.

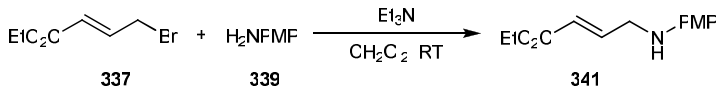
Data for **329**: IR (film) 3446 (OH), 2935, 1730 (C=O), 1514, 1466, 1373, 1242, 1184, 1038, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85-6.82 (2H, m, Ar**H**), 6.70-6.68 (2H, m, Ar**H**), 4.17 (2H, q, *J* = 7.1 Hz, CH_3CH_2O), 3.76 (3H, s, CH_3O), 3.56-3.49 (1H, m, $CHCH_2N$), 3.47-3.33 (2H, m, $CHCH_2N$ and CH_2CH_2N), 3.28-3.20 (1H, m, CH_2CH_2N), 2.72 (1H, app dd, *J* = 10.3, 3.8 Hz, $CHCH_2N$), 2.29-2.21 (1H, m, CH_2CH_2N), 2.07-2.02 (2H, m, $O=CCH_2CH$), 1.93-1.82 (1H, m, CH_2CH_2N), 1.30 (3H, s, CH_3COH), 1.25 (3H, t, *J* = 7.1 Hz, CH_3CH_2O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.3 (C), 151.5 (C), 144.2 (C), 114.8 (2 x CH), 113.8 (2 x CH), 73.8 (C), 60.7 (CH_2), 55.8 (CH_3), 54.5 (CH), 47.6 (CH_2), 45.4 (CH_2), 40.4 (CH_2), 27.3 (CH_2), 24.4 (CH_3), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{26}NO_4$ $[M+H]^+$: 308.1856, found: 308.1849.

(E)-4-Benzylamino-but-2-enoic acid ethyl ester (340).



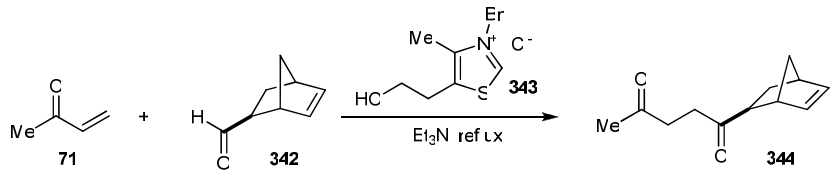
To a stirred solution of benzylamine (**338**) (3.39 mL, 31.10 mmol), in CH_2Cl_2 (30 mL) at 0 °C was added ethyl-4-bromocrotonate (75% pure) (**337**) (2.80 mL, 15.50 mmol) dropwise over 5 min. The reaction was stirred at 0 °C for 30 min and then at room temperature for 21 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the secondary amine **340** (1.690 g, 43%) as a yellow oil. IR (film) 2981, 1717 (C=O), 1453, 1367, 1269, 1173, 1038, 983, 741, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.19 (5H, m, Ar**H**), 6.99 (1H, dt, *J* = 15.7, 5.4 Hz, $CH=CHCH_2$), 5.99 (1H, dt, *J* = 15.7, 1.8 Hz, $CH=CHCH_2$), 4.18 (1H, q, *J* = 7.1 Hz, CH_3CH_2O), 3.79 (2H, s, $PhCH_2N$), 3.40 (2H, dd, *J* = 5.4, 1.8 Hz, $OOCCH=CHCH_2$), 1.46 (1H, s, N**H**), 1.27 (3H, t, *J* = 7.1 Hz, CH_3CH_2O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.4 (C), 146.6 (CH), 139.8 (C), 128.4 (2 x CH), 128.0 (2 x CH), 127.0 (CH), 121.6 (CH), 60.2 (CH_2), 53.2 (CH_2), 49.5 (CH_2), 14.2 (CH_3). These spectral data are consistent with those reported previously.[92]

(E)-4-(4-Methoxy-phenylamino)-but-2-enoic acid ethyl ester (341).



To a stirred solution of *p*-anisidine (**339**) (5.00 g, 40.60 mmol), Et_3N (2.83 mL, 203 mmol), in CH_2Cl_2 (30 mL) was added ethyl-4-bromocrotonate (75% pure) (**337**) (7.34 mL, 40.60 mmol) dropwise over 5 minutes at 0 °C. The reaction was stirred at 0 °C for 30 min and then at room temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), and the mixture was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the secondary amine **341** (1.69 g, 18%) as an orange oil. IR (film) 2982, 2832, 1718 (C=O), 1514, 1369, 1235, 1178, 1037, 965, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (1H, dt, *J* = 15.7, 4.7 Hz, CH=C**H**CH_2), 6.83 – 6.76 (2H, m, Ar**H**), 6.62 – 6.53 (2H, m, Ar**H**), 6.05 (1H, dt, *J* = 15.7, 2.0 Hz, C**H**=$CHCH_2$), 4.19 (2H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}_2$), 3.90 (2H, dd, *J* = 4.7, 2.0 Hz, CH=CHC$\mathbf{H}_2$), 3.75 (3H, s, C$\mathbf{H}_3$O), 1.28 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.3 (C), 152.4 (C), 145.8 (CH), 141.1 (C), 114.9 (2 x CH_2), 114.1 (2 x CH_2), 60.3 (CH_2), 55.7 (CH_3), 45.7 (CH_2), 14.2 (CH_3). These spectral data are consistent with those reported previously.[93]

1-Bicyclo[2.2.1]hept-5-en-2-yl-pentane-1,4-dione (344).



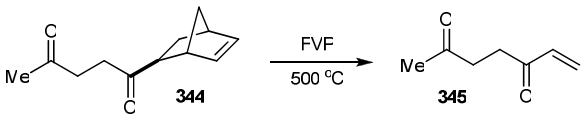
To a stirred solution of bicycle[2.2.1]hept-5-en-2-yl-octan-1,4-dione (**342**) (9.71 mL, 81.90 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**343**) (1.03g, 4.1 mmol) in Et_3N (5.70 mL, 40.9 mmol) was added methyl vinyl ketone (**71**) (6.64 mL, 81.9 mmol). The reaction was stirred at reflux for 24 h and then the

temperature was lowered and CH_2Cl_2 (30 mL) was added. The organic phase was washed with HCl (1 M aqueous solution, 30 mL) and brine (30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford **344** as a yellow oil (8.20 g, 52%) as a mixture of *endo/exo*-isomers that were used without further purification.

Data for major diastereomer: IR (film) 2972, 2871, 1708 (C=O), 1400, 1362, 1167, 1099, 1011, 721, 591 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.14-6.11 (1H, m, CH=C**H**), 5.84-5.83 (1H, m, C**H**=CH), 3.28-3.25 (1H, m, COC**H**), 3.09-3.00 (1H, m, COCHC**H**), 2.88-2.86 (1H, m, CH=CHC**H**), 2.76-2.63 (4H, m, COC$\mathbf{H}_2$C$\mathbf{H}_2$CO), 2.16 (3H, s, C$\mathbf{H}_3$CO), 1.78-1.69 (1H, m, COCHC$\mathbf{H}_2$), 1.44-1.40 (1H, m, COCHC$\mathbf{H}_2$), 1.32-1.30 (2H, m COCHCHC$\mathbf{H}_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.3 (C), 207.2 (C), 137.6 (CH), 131.3 (CH), 51.3 (CH), 49.8 (CH_2), 46.0 (CH), 42.6 (CH), 36.8 (CH_2), 35.3 (CH_2), 29.9 (CH_3), 27.4 (CH_2). These spectral data are consistent with those reported previously.[94]

Data for minor diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 2.19 3H, s, C$\mathbf{H}_3$CO); Due to considerable overlap of signals it was not possible to assign the remainder of the spectrum. ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 211.1 (C), 206.0 (C), 138.1 (CH), 135.8 (CH), 53.4 (CH), 50.6 (CH_2), 45.9 (CH), 45.6 (CH), 41.6 (CH), 37.0 (CH_2), 36.0 (CH_2), 29.2 (CH_3). These spectral data are consistent with those reported previously.[93]

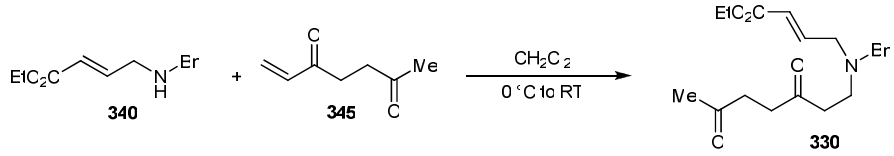
Hept-6-ene-2,5-dione (345).



Flash Vacuum Pyrolysis (FVP) of **344** (4 g, 20.83 mmol), T_f 500 °C, Ti 70-96 °C P 2.3 x 10^{-2} Torr, t 4 h provided the dicarbonyl **345** (2.33 g, 89%) as a yellow oil. IR (film) 2911, 1718 (C=O), 1684, 1617, 1400, 1362, 1164, 1102, 990, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (1H, dd, *J* = 17.7, 9.8 Hz, C**H**=CHH), 6.20 (1H, dd, *J* = 17.7, 1.8 Hz, CH=C**H**H), 5.82 (1H, dd, *J* = 9.8, 1.8 Hz, CH=CH**H**), 2.87-2.81 (2H, m, CH_3O=C$\mathbf{H}_2CH_2C$=O), 2.74-2.69 (2H, m, CH_3O=CH_2C$\mathbf{H}_2$C=O), 2.16 (3H, s,

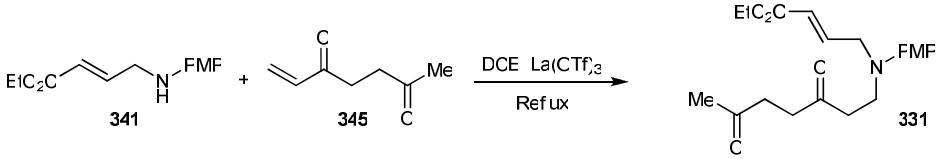
C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 206.9 (C), 198.8 (C), 136.3 (CH), 128.2 (CH), 36.6 (CH_2), 33.0 (CH_2), 29.8 (CH_3). These spectral data are consistent with those reported previously.[95]

(E)-4-[Benzyl-(3,6-dioxo-heptyl)-amino]-but-2-enoic acid ethyl ester (330).



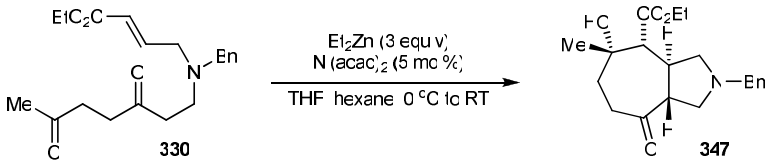
To a stirred solution of amine **340** (1.39 g, 6.30 mmol), in CH_2Cl_2 (17 mL) at 0 °C was added α,β-unsaturated ketone **345** (1.00 g, 7.90 mmol) dropwise over 10 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 24 h followed by removal of the CH_2Cl_2 *in vacuo*. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) afforded the cyclisation precursor **330** (1.861 g, 86%) as a yellow oil. IR (film) 2906, 2810, 1717 (C=O), 1367, 1267, 1177, 1096, 1037, 742, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (5H, m, Ar**H**), 6.93 (1H, dt, *J* = 15.7, 6.0 Hz, CH=C**H**CH_2N), 5.98 (1H, dt, *J* = 15.7, 1.6 Hz, C**H**=$CHCH_2$N), 4.19 (2H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}_2$), 3.58 (2H, s, N$C\mathbf{H}_2$Ph), 3.20 (2H, dd, *J* = 6.0, 1.6 Hz, CH=CHC$\mathbf{H}_2$N), 2.80 (2H, t, *J* = 7.0 Hz, $NCH_2C\mathbf{H}_2COCH_2CH_2CO$), 2.71-2.62 (6H, m, N$C\mathbf{H}_2CH_2COC\mathbf{H}_2C\mathbf{H}_2$CO), 2.18 (3H, s, C**H**$_3$CO), 1.30 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 208.0 (C), 206.9 (C), 166.0 (C), 145.7 (CH), 138.5 (CH), 128.6 (2 x CH), 128.2 (2 x CH), 127.0 (CH), 122.9 (CH), 60.2 (CH_2), 58.4 (CH_2), 54.5 (CH_2), 48.6 (CH_2), 40.8 (CH_2), 36.7 (CH_2), 36.1 (CH_2), 29.8 (CH_3), 14.1 (CH_3); HRMS (EI) Exact mass calcd for $C_{20}H_{28}NO_4$ $[M+H]^+$: 346.2027, found: 346.2013.

(Z)-4-[(3,6-Dioxo-heptyl)-(4-methoxy-phenyl)-amino]-but-2-enoic acid ethyl ester (331)



To a stirred solution of **341** (90 mg, 0.38 mmol), $La(OTf)_3$ (20 mg, 0.035 mmol), in DCE (6 mL) was added α,β-unsaturated ketone **345** (44 mg, 0.35 mmol). The reaction was stirred at 83 °C for 22 h after which the $La(OTf)_3$ was removed through a plug of silica and the DCE was removed *in vacuo*. The residue was purified by column chromatography (hexane→30% EtOAc/hexane) affording cyclisation precursor **331** (73 mg, 58%) as a yellow oil. IR (film) 2905, 2834, 1716 (C=O), 1512, 1367, 1177, 1097, 1038, 816, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (1H, dt, *J* = 15.1, 4.6 Hz, CH=C**H**CH_2N), 6.81 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.63 (2H, d, *J* = 9.1 Hz, Ar**H**), 5.88 (1H, dt, *J* = 15.1, 1.9 Hz, C**H**=CHCH_2N), 4.17 (2H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}_2$), 3.99 (2H, dd, *J* = 2.7, 1.9 Hz, CH=CH$C\mathbf{H}_2$N), 3.75 (3H, s, CH_3O), 3.56 (2H, t, *J* = 6.9 Hz, $NCH_2C\mathbf{H}_2COCH_2CH_2CO$), 2.79-2.61 (6H, m, $NC\mathbf{H}_2CH_2COC\mathbf{H}_2C\mathbf{H}_2CO$), 2.19 (3H, s, $C\mathbf{H}_3CO$), 1.27 (3H, t, *J* = 7.1 Hz, $C\mathbf{H}_3CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 208.2 (C), 207.0 (C), 166.2 (C), 152.1 (C), 145.0 (CH), 141.7 (C), 122.0 (CH), 114.9 (2 x CH), 114.8 (2 x CH), 60.3 (CH_2), 55.7 (CH_3), 53.1 (CH_2), 46.4 (CH_2), 40.5 (CH_2), 36.8 (CH_2), 36.7 (CH_2), 29.8 (CH_3), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$: 362.1962, found: 362.1964.

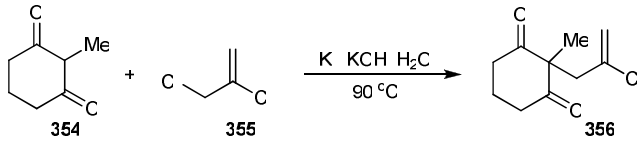
(3aS,4R,5S,8aR)-2-Benzyl-5-hydroxy-5-methyl-decahydro-cyclohepta[*c*]pyrrole-4-carboxylic acid ethyl ester (347).



A solution of **330** (250 mg, 0.70 mmol), and $Ni(acac)_2$ (47 mg, 0.07 mmol), in THF (5.0 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 2.17 mL, 2.17 mmol) was added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 20 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (5 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the

residue by column chromatography (hexane→50% EtOAc/hexane) afforded the bicyclic product **347** (37 mg, 15%) as a white solid. Slow evaporation of a hexane solution of **347** provided colourless crystals that were suitable for X-ray crystallography. m.p. 109-111 °C; IR ($CHCl_3$) 3496, 2972, 2799, 1704 (C=O), 1454, 1374, 1180, 1019, 887, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.20 (5H, m, Ar**H**), 4.24-4.10 (2H, m, OC**H**$_2$CH$_3$), 3.87 (1H, s, O**H**), 3.58 (2H, s, NC**H**$_2$Ph), 3.36-3.33 (1H, m, C**H**CO$_2$Et), 3.11-2.93 (2H, m, HOCCH$_2$C**H**$_2$), 2.75-2.64 (2H, m, CH$_2$C=OC**H**C**H**), 2.55-2.47 (2H, m, HOCC**H**$_2$CH$_2$), 2.34-2.27 (2H, m, O=CCHC**H**$_2$N), 1.92-1.89 (2H, m, HOCCHCH**H**$_2$N), 1.26 (3H, s, C**H**$_3$C), 1.23 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 210.1 (C), 175.2 (C), 138.3 (C), 128.7 (2 x CH), 128.2 (2 x CH), 127.0 (CH), 70.5 (C), 61.0 (CH_2), 60.1 (CH_2), 59.0 (CH), 58.2 (CH_2), 55.4 (CH), 53.0 (CH_2), 38.7 (CH), 36.2 (CH_2), 35.5 (CH_2), 30.8 (CH_3), 14.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{28}NO_4$ $[M+H]^+$: 346.2017, found: 346.2013.

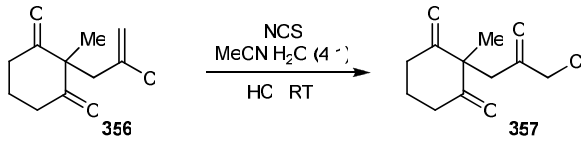
2-(2-Chloro-allyl)-2-methyl-cyclohexane-1,3-dione (356).



To a stirred solution of 2-methyl-1,3-cyclohexadiene (**354**) (5.00 g, 39.60 mmol), KI (1.32 g, 7.90 mmol), KOH (2.67 g, 47.60 mmol), in H_2O (11 mL) was added allylchloride **355** (4.38 mL, 47.60 mmol). The reaction was stirred at 90 ^oC for 4 hours after which the reaction was cooled, diluted with ether and then washed with water. The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) afforded the monochloro product **356** (2.98 g, 38%); as a yellow oil. IR (film) 2964, 1696 (C=O), 1635, 1457, 1374, 1319, 1131, 1023, 913, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (1H, d, *J* = 1.4 Hz, C=C**H**H), 5.13 (1H, d, *J* = 1.4 Hz, C=CH**H**), 2.97 (2H, s, CH$_3$CC**H**$_2$), 2.80-2.60 (4H, m, C**H**$_2$CH$_2$C**H**$_2$), 2.14-1.87 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.26 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.6 (2 x

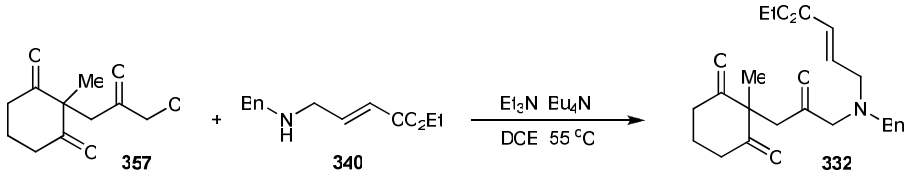
C), 137.4 (C), 116.3 (CH), 62.9 (C), 45.0 (CH_2), 38.3 (2 x CH_2), 23.1 (CH_3), 17.4 (CH_2). These spectral data are consistent with those reported previously.[96]

2-(3-Chloro-2-oxo-propyl)-2-methyl-cyclohexane-1,3-dione (357).



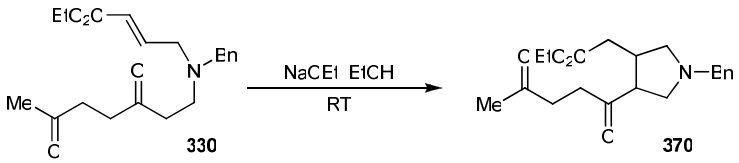
To a stirred solution of monochloro **356** (1.00 g, 4.99 mmol), in H_2O (5 mL) and MeCN (20 mL) was added *N*-chlorosuccinimide (883 mg, 6.48 mmol) in one portion followed by HCl (conc. solution, 20 μL). The reaction was stirred at room temperature for 22 h and then quenched with saturated aqueous $NaSO_3$ solution (10 mL). Ether (20 mL) was added to the reaction mixture which was then washed with $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* affording α-chloroketone **357** (890 mg, 82%) as a white solid which was used without further purification. IR ($CHCl_3$) 2934, 1695 (C=O), 1456, 1388, 1285, 1138, 1095, 1024, 867, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.07 (2H, s, CC**H**$_2$), 3.32 (2H, s, C**H**$_2$Cl) 2.72-2.68 (4H, m, C**H**$_2$CH$_2$C**H**$_2$), 2.23-2.03 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.27 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.9 (2 x C), 201.1 (C), 60.6 (C), 47.5 (C), 45.8 (CH_2), 37.5 (2 x CH_2), 23.2 (CH_3), 17.3 (CH_2); HRMS (ES) Exact mass calcd for $C_{10}H_{13}ClO_3$ $[M]^+$: 216.0548, found: 216.0545.

(E)-4-{Benzyl-[3-(1-methyl-2,6-dioxo-cyclohexyl)-2-oxo-propyl]-amino}-but-2-enoic acid ethyl ester (332)



To a stirred solution of **340** (500 mg, 2.28 mmol), **357** (494 mg, 2.28 mmol), Bu_4NI (927 mg, 2.51 mmol,), in DCE (15 mL), was added Et_3N (636 μL, 4.57 mmol). The reaction mixture was stirred at 55 ^oC for 24 h. H_2O was added (20 mL) and the reaction mixture extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the cyclisation precursor **332** (480 mg, 44%) as a yellow oil. IR ($CHCl_3$) 2931, 1714 (C=O), 1454, 1369, 1275, 1179, 1094, 1025, 744, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.24 (5H, m, Ar**H**), 6.96 (1H, dt, *J* = 15.7, 6.0 Hz, CH=C**H**CH_2N), 6.03 (1H, dt, *J* = 15.7, 1.6 Hz, C**H**=$CHCH_2N$), 4.20 (2H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}_2$), 3.64 (2H, s, $NC\mathbf{H}_2Ar$), 3.30 (2H, dd, *J* = 6.0, 1.5 Hz, CH=$CHC\mathbf{H}_2N$), 3.26 (2H, s, $C\mathbf{H}_2CCH_3$), 3.21 (2H, s, $NC\mathbf{H}_2CO$), 2.74-2.68 (4H, m, $C\mathbf{H}_2CH_2C\mathbf{H}_2$), 2.81-2.04 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 1.30 (3H, t, *J* = 7.1 Hz, $C\mathbf{H}_3CH_2$), 1.26 (3H, s, $C\mathbf{H}_3C$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 210.4 (C), 208.3 (C), 166.1 (C), 145.1 (CH), 137.8 (C), 128.9 (2 x CH), 128.4 (2 x CH), 127.4 (CH), 123.5 (CH), 61.9 (CH_2), 60.3 (CH_2), 60.1 (C), 58.4 (CH_2), 54.8 (CH_2), 46.8 (CH_2), 37.5 (2 x CH_2), 23.1 (CH_3), 17.4 (CH_3), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2118, found: 400.2112.

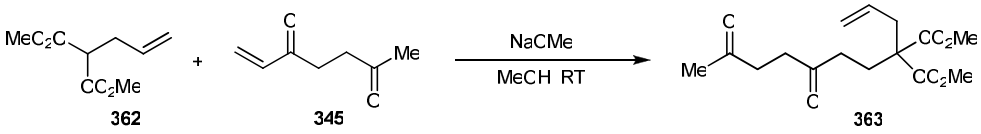
[1-Benzyl-4-(4-oxo-pentanoyl)-pyrrolidin-3-yl]-acetic acid ethyl ester (370).



To a stirred solution of **330** (100 mg, 0.29 mmol), in EtOH (2 mL) was added, under open flask conditions, NaOEt (10 mg, 0.14 mmol). The reaction was stirred at room temperature for 15 mins and then the EtOH was removed *in vacuo*. Removal of the NaOEt through a plug of silica followed by purification of the residue by column chromatography (hexane→40% EtOAc/hexane) afforded the monocyclic product **370** (61 mg, 61%) as a colourless oil. IR (film) 2918, 2796, 1714 (C=O), 1317, 1255, 1163, 1099, 1030, 744, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m,

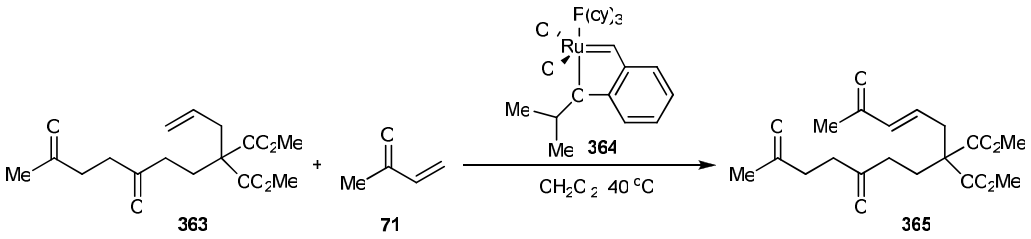
Ar**H**), 4.10 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.60 (2H, s, C**H**$_2$Ph), 2.96-2.85 (3H, m, CH$_3$C=OC**H**$_2$CH$_2$ and O=CC**H**CHHN), 2.78-2.66 (5H, m, CH$_3$C=OCH$_2$C**H**$_2$ and O=CC**H**$_2$CH and O=CCH$_2$C**H**), 2.63-2.60 (1H, m, O=CCHC**H**HN), 2.54-2.41 (3H, m, O=CCHCH**H**N and O=CCH$_2$CHC**H**$_2$N), 2.18 (3H, s, C**H**$_3$C=O), 1.23 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 208.9 (C), 207.0 (C), 172.3 (C), 138.7 (C), 128.5 (2 x CH), 128.2 (2 x CH), 126.9 (CH), 60.4 (CH$_2$), 59.6 (CH$_2$), 59.4 (CH$_2$), 56.2 (CH$_2$), 55.9 (CH), 39.4 (CH$_2$), 36.9 (CH$_2$), 36.5 (CH), 35.2 (CH$_2$), 29.9 (CH$_3$), 14.1 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{20}H_{28}NO_4$ [M+H]$^+$: 346.2013, found: 346.2016.

2-Allyl-2-(3,6-dioxo-heptyl)-malonic acid dimethyl ester (363)



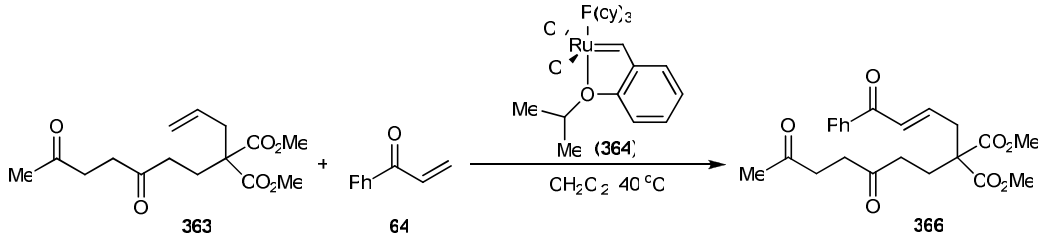
To a stirred solution of diester **362** (1.00 g, 5.80 mmol), dicarbonyl **345** (733 mg, 5.80 mmol), in MeOH (40 mL) was added NaOMe (395 mg, 5.8 mmol) in small portions over a 20 minute period under open flask conditions. The reaction was stirred at room temperature 30 then H_2O was added (40 mL) and the reaction mixture extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) afforded the Michael product **363** (1.354 g, 71%) as a colourless oil. IR (film) 2954, 2910, 1732 (C=O), 1437, 1367, 1213, 1099, 999, 928, 663 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.69-5.57 (1H, m, CH$_2$=C**H**CH$_2$), 5.12-5.06 (2H, m, C**H**$_2$=CHCH$_2$), 3.70 (6H, s, (CO$_2$C**H**$_3$)$_2$), 2.71-2.60 (6H, m, COC**H**$_2$C**H**$_2$CO and CH$_2$=CHC**H**$_2$), 2.47 (2H, t, *J* = 8.2 Hz, COC**H**$_2$CH$_2$C), 2.16 (3H, s, COC**H**$_3$), 2.13 (2H, t, *J* = 8.2 Hz, COCH$_2$C**H**$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 207.7 (C), 207.0 (C), 171.3 (2 x C), 132.0 (CH), 119.3 (CH$_2$), 56.8 (C), 52.4 (2 x CH$_3$), 38.1 (CH$_2$), 37.6 (CH$_2$), 36.8 (CH$_2$), 36.0 (CH$_2$), 29.8 (CH$_3$), 26.5 (CH$_2$); HRMS (ES) Exact mass calcd for $C_{15}H_{23}O_6$ [M+H]$^+$: 299.1489, found: 299.1488.

2-(3,6-Dioxo-heptyl)-2-((Z)-4-oxo-pent-2-enyl)-malonic acid dimethyl ester (365)



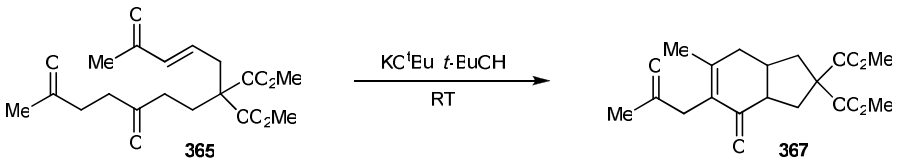
To a stirred solution of **363** (100 mg, 0.33 mmol), Hoveyda-Grubbs catalyst (**364**) (2.10 mg, 0.0033 mmol), in CH_2Cl_2 (5 mL) was added methyl vinyl ketone (**71**) (108 μL, 1.34 mmol). The reaction was stirred at 40 °C for 24 h and the CH_2Cl_2 was removed *in vacuo*. Removal of the Hoveyda-Grubbs catalyst through a plug of silica followed by purification by column chromatography (hexane→50% EtOAc/hexane) afforded cyclisation precursor **365** (94 mg, 84%) as a colourless oil. IR (film) 2956, 2914, 1732 (C=O), 1676 (C=O), 1435, 1363, 1257, 1178, 1095, 985 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.61 (1H, dt, *J* = 15.9, 7.5 Hz, CH=C**H**CH_2N), 6.06 (1H, d, *J* = 15.9 Hz, C**H**=CHCH_2N), 3.71 (6H, s, ($CO_2C\mathbf{H}_3$)$_2$), 2.74 (2H, d, *J* = 7.5 Hz, CH=CHC**H**$_2$N), 2.69 (2H, dd, *J* = 4.3, 2.4 Hz, CO**CH**$_2$$CH_2$$COCH_3$), 2.62 (2H, dd, *J* = 4.3, 2.4 Hz, $COCH_2$C**H**$_2$$COCH_3$), 2.50 (2H, t, *J* = 8.1 Hz, CCH_2C**H**$_2$CO), 2.21 (3H, s, C**H**$_3$COCH=CH), 2.16 (3H, s, C**H**$_3$$COCH_2$), 2.14 (2H, t, *J* = 8.1 Hz, CC**H**$_2$$CH_2$CO; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 207.3 (2 x C), 206.9 (C), 197.9 (C), 170.7 (C), 141.1 (CH), 134.5 (CH), 56.7 (CH), 52.6 (2 x CH_3), 37.6 (CH_2), 36.9 (2 x CH_2), 36.0 (CH_2), 29.8 (CH_3), 27.0 (CH_2), 26.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{25}O_7$ $[M+H]^+$: 341.1595, found: 341.1598.

2-(3,6-Dioxo-heptyl)-2-((Z)-4-oxo-4-phenyl-but-2-enyl)-malonic acid dimethyl ester (366)



To a stirred solution of **363** (500 mg, 1.67 mmol), Hoveyda-Grubbs catalyst (**364**) (10.50 mg, 0.017 mmol), in CH_2Cl_2 (15 mL) was added phenyl vinyl ketone (**64**) (441 mg, 3.34 mmol). The reaction was stirred at 40 ^oC for 48 h and the CH_2Cl_2 was removed *in vacuo*. Removal of the Hoveyda-Grubbs catalyst through a plug of silica followed by purification by column chromatography (hexane→40% EtOAc/hexane) afforded cyclisation precursor **366** (265 mg, 39%) as a brown oil. IR (film) 2954, 1732 (C=O), 1672 (C=O), 1622, 1446, 1356, 1279, 1203, 1012, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91-7.89 (2H, m, Ar**H**), 7.58-7.55 (1H, m, C**H**=CHCH$_2$), 7.48-7.45 (2H, m, Ar**H**), 6.93-6.80 (2H, m, CH=C**H**CH$_2$ and Ar**H**), 3.74 (6H, s, (C(COOC**H**$_3$)$_2$), 2.87 (2H, d, *J* = 7.2 Hz, CH=CHC**H**$_2$N), 2.71-2.64 (4H, m, COC**H**$_2$C**H**$_2$COCH$_3$), 2.55 (2H, t, *J* = 7.6 Hz, CCH$_2$C**H**$_2$CO), 2.20 (2H, t, *J* = 7.6 Hz, CC**H**$_2$CH$_2$CO), 2.17 (3H, s, C**H**$_3$COCH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 207.4 (2 x C), 190.1 (C), 170.8 (2 x C), 142.2 (CH), 137.4 (C), 132.8 (CH), 129.6 (CH), 128.6 (CH), 128.6 (4 x CH), 56.8 (C), 52.7 (2 x CH_3), 37.8 (CH_2), 37.3 (CH_2), 36.9 (CH_2), 36.0 (CH_2), 26.8 (CH_3), 27.2 (CH_2); HRMS (ES) Exact mass calcd for $C_{22}H_{27}O_7$ $[M+H]^+$: 403.1751, found: 403.1745.

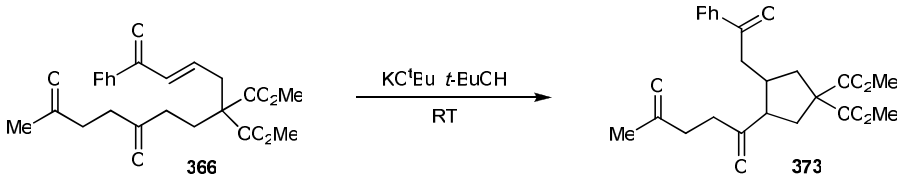
6-Methyl-4-oxo-5-(2-oxo-propyl)-1,3,3a,4,7,7a-hexahydro-indene-2,2-dicarboxylic acid dimethyl ester (367)



To a stirred solution of cyclisation precursor **365** (102 mg, 0.30 mmol), in *t*-BuOH (3 mL) was added, under open flask conditions, KO^{t}Bu (34 mg, 0.30 mmol). The reaction was stirred at room temperature for 30 min then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the bicyclic product **367** (19 mg, 20%) as a colourless oil. IR (film) 3583, 2922, 2852, 1730 (C=O), 1653, 1433, 1358, 1263, 1161, 665 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 3.74 (3H, s, OC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 3.48-3.39 (2H, m, $CH_3COC\mathbf{H}_2$), 2.77-2.59 (5H, m, $C\mathbf{H}_2C\mathbf{H}CHC\mathbf{H}_2C$), 2.40-2.31 (2H, m, $CH_3CC\mathbf{H}_2$), 2.25-2.19 (1H, m, $CH_2CHC\mathbf{H}CH_2C$), 2.16 (3H, s, $C\mathbf{H}_3COCH_2$), 1.88 (3H, s, $C\mathbf{H}_3CCH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.7 (C), 197.3 (C), 172.8 (C), 172.3 (C), 155.4 (C), 128.6 (C), 58.6 (C), 52.9 (2 x CH_3), 47.6 (CH), 40.3 (CH_2), 39.1 (CH_2), 36.8 (CH), 36.2 (CH_2), 33.4 (CH_2), 29.6 (CH_3), 22.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{23}O_6$ $[M+H]^+$: 323.1489, found: 323.1494.

3-(4-Oxo-pentanoyl)-4-(2-oxo-2-phenyl-ethyl)-cyclopentane-1,1-dicarboxylic acid dimethyl ester (373)



To a stirred solution of cyclisation precursor **366** (121 mg, 0.30 mmol), in *t*-BuOH (3 mL) was added, under open flask conditions, KO^{t}Bu (34 mg, 0.30 mmol). The reaction was stirred at room temperature for 15 min and then quenched with saturated aqueous NH_4Cl solution (10 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→30% EtOAc/hexane) afforded the monocyclic product **373** (14 mg, 11%); as a colourless oil. IR (film) 2954, 2918, 1732 (C=O), 1435, 1365, 1259, 1167, 1001, 914, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.93 (2H, m, Ar**H**), 7.57-7.55 (1H, m, Ar**H**), 7.47-7.44 (2H, m, Ar**H**), 3.75 (3H, s, OC**H**$_3$), 3.73 (3H, s, OC**H**$_3$), 3.26-3.22 (1H, m, COC**H**), 2.99-2.84 (3H, m, $CH_3COC\mathbf{H}_2C\mathbf{H}_2CH_2CO$), 2.80-2.67 (6H, m, $COC\mathbf{H}_2C\mathbf{H}CHC\mathbf{H}_2$ and $CH_3COC\mathbf{H}_2CH_2CO$), 2.41-2.37 (1H, m, $COCH_2CHC\mathbf{H}_2C$), 2.19 (3H, s, $C\mathbf{H}_3CO$), 2.01-1.96 (1H, m, $COCH_2CHC\mathbf{H}_2C$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.3 (C), 207.1 (C), 198.9 (C), 172.6 (C), 171.8 (C), 136.7 (C), 133.1 (CH), 128.6 (2 x CH), 128.1 (2 x CH), 59.1 (C), 56.4 (CH), 52.9 (CH_3), 52.8 (CH_3), 43.1 (CH_2), 39.5 (CH), 37.5 (CH_2), 37.4 (CH_2), 37.1 (CH_2), 35.5

(CH_2), 29.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{30}NO_7$ $[M+H]^+$: 420.2019, found: 420.2017.

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5.4 Appendix 1

List of publications

1) **Diastereoselective Intermolecular Cobalt-Catalyzed Reductive Aldol Reactions of α,β-Unsaturated Amides with Ketones,** Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. *Org. Lett.* **2007**, *9*, 4367.

2) **Racemic and Asymmetric Cobalt-Catalysed Reductive Aldol Couplings of α,β-Unsaturated Amides with Ketones**, Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. *Tetrahedron* **2008**, *64*, 7729.

Diastereoselective Intermolecular Cobalt-Catalyzed Reductive Aldol Reactions of α,β-Unsaturated Amides with Ketones

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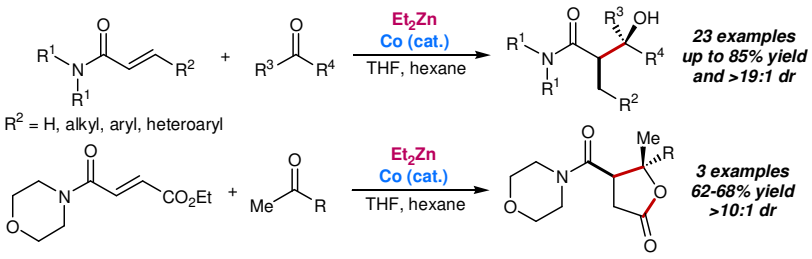
Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



Under cobalt catalysis, diethylzinc mediates the conjugate reduction of α,β-unsaturated amides to produce ethylzinc enolates that react with ketones in situ to produce tertiary alcohol-containing aldol products with up to >19:1 diastereoselectivity.

Zinc enolates comprise an important class of reagents for organic synthesis, readily reacting with a range of electrophiles[13,14,15] and exhibiting lower basicity and greater functional group compatibility compared to their alkali metal counterparts. There are several common methods to access zinc enolates using stoichiometric zinc sources.[16,17]

(13) For the reaction of zinc enolates with aldehydes and ketones, see: (a) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210–1211. For reviews of the Reformatsky reaction, see: (b) Fürstner, A. *Synthesis* **1989**, 571–590. (c) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325–9374. (d) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2568–2571.

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(15) For the use of zinc enolates in palladium-catalyzed α-arylations, see: (a) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976–4985. (b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177. (c) Bentz, E.; Moloney, M. G.; Westaway, S. M. *Tetrahedron Lett.* **2004**, *40*, 7395–7397.

(16) For other recent methods of stoichiometric zinc enolate formation not discussed above, see: (a) Ikeda, Z.; Hirayama, T.; Matsubara, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8200–8203. (b) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *16*, 4105–4108. (c) Hlavinka, M. L.; Hagadorn, J. R. *Tetrahedron Lett.* **2006**, *47*, 5049–5053. (d) Hlavinka, M. L.; Greco, J. F.; Hagadorn, J. R. *Chem. Commun.* **2005**, 5304–5306.

(17) For selected examples of catalytic zinc enolate generation using *substoichiometric* quantities of chiral bimetallic zinc complexes, see: (a) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M.. *J. Am. Chem. Soc.* **2004**, *126*, 8777–8785. (b) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582–2590. (c) Kumagai,

The first method involves the transmetalation of an alkali metal enolate with a zinc halide, which necessitates the use of strong alkali metal amide bases at low temperatures in a prior enolization step that may be accompanied by regioselectivity problems when more than one site of enolization is available.

The second method involves the reaction of a suitable zinc source (zinc powder, organozinc reagents) with an α-halocarbonyl compound, with or without catalysis.[13] Advantages of this method are the use of milder, less basic conditions, often complete regioselectivity, and the ability to have the electrophile present in situ. The utility of this methodology is evidenced by the Reformatsky reaction and its variants, which are still widely practiced in synthesis today.[13] However, the use of α-halocarbonyls compounds as zinc enolate precursors is not without limitations. Although simple α-halocarbonyls are readily available, more complex substrates require the installation of the halide in a separate step, which may pose problems when sensitive functional groups are present.

A third method to prepare zinc enolates is via the catalytic conjugate addition of organozinc reagents to an α,β-unsaturated carbonyl compound.[18] While benefiting from the advantages of chemically robust, readily available precursors, and high regioselectivity of enolate formation under mild conditions, the α,β-unsaturated carbonyl compounds that may be employed are often restricted to enones. More synthetically versatile but less reactive α,β-unsaturated carboxylic acid derivatives remain challenging substrates for catalytic organozinc conjugate additions.[19] Furthermore, this method necessitates the formation of a carbon–carbon bond and often a new stereogenic center. Although desired in some cases, other synthetic applications may not require this increase in complexity. Therefore, the development of an analogous method that results in the formation of a *carbon–hydrogen bond* using α,β-unsaturated carboxylic acid derivatives should be of utility.

We recently reported a method for the generation of zinc enolates that meets these criteria.[20] In the presence of a substoichiometric quantity of a cobalt salt, diethylzinc mediates the conjugate reduction of α,β-unsaturated amides **1** to form ethylzinc enolates **2** that participate in high-yielding diastereoselective aldol cyclizations with tethered ketone electrophiles (Scheme 1). Herein, we report that the Co/Et_2Zn system is able to promote the corresponding *intermolecular* reductive aldol reactions[21] of α,β-unsaturated amides with ketones[22] in situ to furnish tertiary alcohol-containing aldol products.

Scheme 1. Cobalt-Catalyzed Reductive Aldol Cyclization

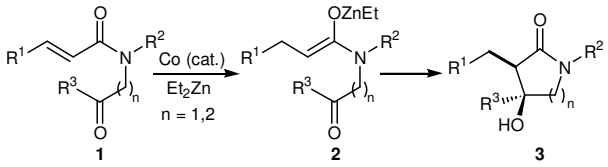

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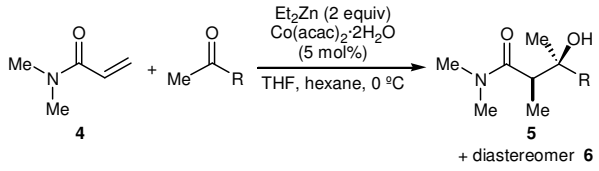
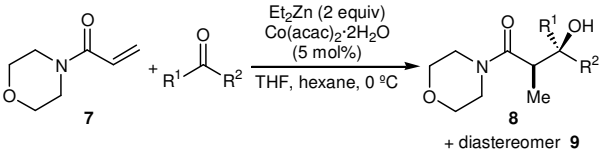
Table 1. Cobalt-Catalyzed Reductive Aldol Reactions of *N*,*N*-Dimethylacrylamide (**4**) with Representative Ketones[a]



entry	R	product(s)	dr[b]	yield(s) (%)[c]
1	Ph	**5a**	5:1	75
2	2-MePh	**5b**	9:1	68
3	4-MePh	**5c**	5.5:1	79
4	4-MeOPh	**5d**	6:1	84
5	2-BrPh	**5e**	7:1	56
6	4-BrPh	**5f**, **6f**	3.5:1	73 (15)
7	2-naphthyl	**5g**	5:1	78
8	2-furyl	**5h**, **6h**	2.5:1	66 (25)

[a] Reactions were conducted using 1.0 mmol of **4** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1–29 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

Table 2. Cobalt-Catalyzed Reductive Aldol Reactions of 4-Acryloylmorpholine (**7**) with Representative Ketones[a]



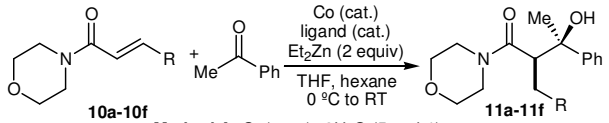
entry	R^1	R^2	product(s)	dr[b]	yield(s) (%)[c]
1	Me	Ph	**8a**	5.5:1	80
2	Me	2-MePh	**8b**	9:1	84
3	Me	4-MeOPh	**8c**	6.5:1	85
4	Me	2-naphthyl	**8d**, **9d**	4.5:1	82 (17)
5	Me	2-furyl	**8e**, **9e**	3:1	72 (22)
6	Me	*i*-Pr	**8f**, **9f**	1:1	33 (31)
7	Me	*i*-Bu	**8g**, **9g**	1:1	35 (36)
8	Et	Ph	**8h**	6:1	75
9	Ph	Ph	**8i**	na	62

[a] Reactions were conducted using 1.0 mmol of **7** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 3–7 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

Our studies commenced with the reactions of a range of ketones with commercially available *N*,*N*-dimethylacrylamide (**4**) (Table 1) and 4-acryloylmorpholine (**7**) (Table 2). Under similar conditions to those employed in our previous study,[20] amides **4** and **7** underwent smooth reductive aldol reactions with a range of acetophenone derivatives containing substituents of varying electronic properties to provide the corresponding aldol products with up to 9:1 diastereomeric ratio and 85% isolated yield of the major diastereomer (Table 1, entries 1–6, and Table 2, entries 1–3). The beneficial effect of *ortho*-substitution in the acetophenone on the diastereoselectivity of the reaction should be noted (Table 1, entries 2 and 5, and Table 2, entry 2). Reactions with ketones containing naphthyl and furyl substituents were successful (Table 1, entries 7–8 and Table 2, entries 4–5), as was reaction of **7** with propiophenone (Table 2, entry 8) and benzophenone (Table 2, entry 9). Although aliphatic ketones were also found to be competent substrates from a reactivity standpoint, their reactions exhibit no diastereoselection (Table 2, entries 6–7).

Table 3 presents the results of reaction of a range of *β*-substituted α,*β*-unsaturated morpholine amides with acetophenone. These data illustrate that substitution at the *β*-position of the unsaturated amide has a beneficial impact on reaction diastereoselectivity (≥ 9:1). Both linear and branched alkyl groups were tolerated (entries 1–3), as were aromatic (entries 4–5) and heteroaromatic (entry 6) substituents. With alkyl-substituted morpholine amides **10a**–**10c**, incomplete conversions were observed using $Co(acac)_2{\cdot}2H_2O$ as the pre-catalyst, but the combination of $CoCl_2$ and Cy_2PPh provided improved results (entries 1–3).[20]

Table 3. Cobalt-Catalyzed Reductive Aldol Reactions of Acetophenone with Representative α,*β*-Unsaturated Morpholine Amides[a]



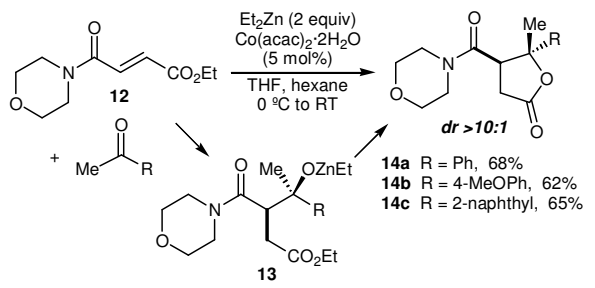
Method A: $Co(acac)_2{\cdot}2H_2O$ (5 mol%)
Method B: $CoCl_2$ (5 mol%), Cy_2PPh (5.5 mol%)

entry	method	R	substrate	product	dr[b]	yield (%)[c]
1	B	Me	**10a**	**11a**	>19:1	76
2	B	*i*-Bu	**10b**	**11b**	>19:1	85
3	B	CH_2CH_2Ph	**10c**	**11c**	16:1	81[d]
4	A	Ph	**10d**	**11d**	>19:1	71
5	A	2-naphthyl	**10e**	**11e**	10:1	74
6	A	2-furyl	**10f**	**11f**	9:1	84

[a] Reactions were conducted using 1.0 mmol of **10a**-**10f** and 1.1 mmol of acetophenone in THF (10 mL) and hexane (2 mL) for 2–6 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer. [d] Yield of a 16:1 inseparable mixture of diastereomers.

Unsaturated amide **12** provided an interesting regiochemical problem, since it contains an α,*β*-unsaturated amide that also forms part of an α,*β*-unsaturated ester. It was therefore of interest to observe whether conjugate reduction would be successful, and if so, whether an amide enolate or an ester enolate would result. In the event, reductive aldol reaction of **12** with a

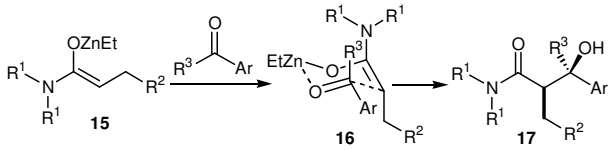
Scheme 2. Reductive Aldol Coupling of **12** with Various Ketones Producing Lactones **14a**-**14c**.



range of methyl ketones provided lactones **14a**–**14c** in 62–68% yield as a result of the intermediate zinc alkoxides **13** cyclizing onto the pendant ethyl ester (Scheme 2). These experiments demonstrate that conjugate reduction of **12** occurred to generate the morpholine amide enolate preferentially.[23]

The diastereochemical outcomes of these reactions[24] are consistent with the participation of *Z*-zinc enolates **15** and chelated chair-like Zimmerman–Traxler transition states[25] in which the larger aromatic substituent of the ketone prefers to reside in a less sterically hindered pseudoequatorial position (as in **16**) (Scheme 3).

Scheme 3. Model for Stereochemical Outcome.



In conclusion, zinc enolates generated through cobalt-catalyzed conjugate reduction of α,*β*-unsaturated amides using diethylzinc as the stoichiometric reductant undergo in situ diastereoselective aldol reactions with ketones to provide tertiary *β*-hydroxycarbonyl compounds. Further applications of this methodology will be reported in due course.

(23) α,*β*-Unsaturated esters do undergo reductive aldol reactions with ketones using Co/Et_2Zn, but with low diastereoselectivities. For example, methyl cinnamate reacts with acetophenone to produce a *ca*. 1:1 mixture of diastereomers.

(24) The relative stereochemistry of the known compound **5a** was assigned by comparison with literature spectral data. The relative stereochemistries of **5c**, **8f**, and **8g** were determined by X-ray crystallography. The stereochemistries of the remaining aldol products were assigned by analogy. See Supporting Information for details.

(25) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material available free of charge via the Internet at http://pubs.acs.org.

Pergamon

TETRAHEDRON

Racemic and asymmetric cobalt-catalysed reductive aldol couplings of α,β-unsaturated amides with ketones

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Abstract

In the presence of diethylzinc as a stoichiometric reductant, substoichiometric quantities of an appropriate cobalt source catalyse diastereoselective reductive aldol coupling reactions of α,β-unsaturated amides with ketones. The use of a readily available oxazolidine as a chiral auxiliary imparts high levels of asymmetric induction in these reactions.

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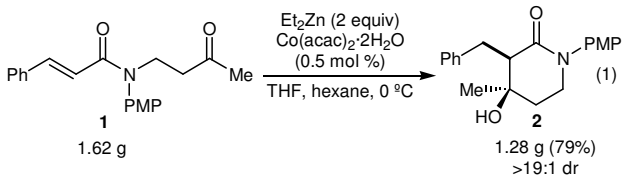
1. Introduction

The reductive aldol reaction, in which an aldehyde or ketone undergoes reaction with an enolate generated in situ by the conjugate reduction of an α,β-unsaturated carbonyl compound, is a powerful and well-established method of carbon–carbon bond-formation.[xcvii,xcviii] Using various metal precatalysts, and stoichiometric reductants that include silanes, triethylborane, and molecular hydrogen, a wide variety of inter- and intramolecular reductive aldol reactions have been described.[xcvii,xcviii] A recent major development in this area is the ability to control the absolute stereochemistry of the products through the use of substoichiometric quantities of chiral metal–ligand complexes.[xcviii]

One contribution to this field from our research group has been the development of both inter- and intramolecular reductive aldol reactions that employ diethylzinc as the stoichiometric reductant, in conjunction with cobalt[xcix] or nickel[c] precatalysts. An advantageous feature of these conditions is the ability to promote high-yielding reactions between β-substituted α,β-unsaturated carboxylic acid derivatives and ketones, reaction partners that are situated on the lower end of the reactivity scale in reductive aldol reactions. In this Article, we provide a full account of the intermolecular reactions[xcixb] promoted by Et_2Zn in combination with a cobalt source,[ci] along with extension to an asymmetric variant using a chiral oxazolidine auxiliary.

2. Results and discussion

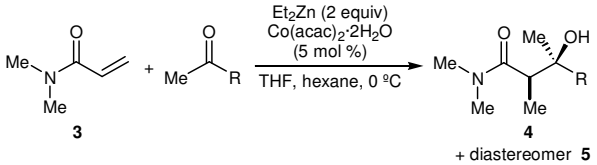
During ongoing efforts to develop new catalyst systems for the diasteroselective synthesis of β-hydroxylactones[c,ciia] and lactams[xcixa,c,ciib] using reductive aldol cyclisations, we recently established the exceptional ability of $Co(acac)_2{\cdot}2H_2O/Et_2Zn$[xcixa] in promoting reactions of substrates that were problematic under previously reported conditions using copper catalysis[cii] (representative example in eq 1).



Whether the $Co(acac)_2{\cdot}2H_2O/Et_2Zn$ combination could also be applied to the corresponding *intermolecular* reductive aldol reactions was an important issue to address, and with this consideration in mind, the reaction of *N*,*N*-dimethylacrylamide (**3**) with acetophenone was conducted. This experiment was successful, and provided the aldol product **4a**[ciii] in 75% yield, accompanied by the diastereomeric product (not shown), in a 5:1 ratio (Table 1, entry 1). The use of 4-acryloylmorpholine (**6**) as the pronucleophilic component provided very similar results (Table 2, entry 1).

Further examination of substrate scope revealed that acetophenone derivatives containing alkyl, methoxy, or bromo substituents were competent electrophiles in these reactions, providing tertiary alcohol-containing aldol products with up to 9:1 diastereomeric ratio and 85% isolated yield of the major diastereomer (Table 1, entries 2–6 and Table 2, entries 1–3). *Ortho*-substitution in the acetophenone was found to result in enhanced levels of diastereoselection (Table 1, entries 2 and 5, and Table 2, entry 2). However, the reaction of 4-nitroacetophenone with **3** provided none of the desired product **4g**, with a complex mixture being obtained instead (Table 1, entry 7). Presumably, the highly electron-deficient nature of

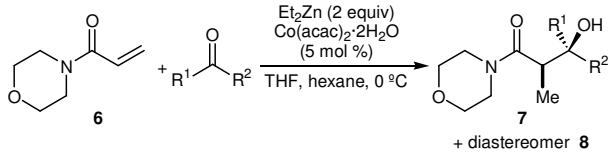
Table 1. Cobalt-catalysed reductive aldol reactions of *N*,*N*-dimethylacrylamide (**3**) with representative ketones[a]



Entry	R	Product(s)	dr[b]	Yield(s) (%)[c]
1	Ph	**4a**	5:1	75
2	2-MePh	**4b**	9:1	68
3	4-MePh	**4c**	5.5:1	79
4	4-MeOPh	**4d**	6:1	84
5	2-BrPh	**4e**	7:1	56
6	4-BrPh	**4f**, **5f**	3.5:1	73 (15)
7	4-NO_2Ph	**4g**	n/a	0[d]
8	2-naphthyl	**4h**	5:1	78
9	2-furyl	**4i**, **5i**	2.5:1	66 (25)
10	CO_2Et	**4j**	n/a	0[d]

[a]Reactions were conducted using 1.0 mmol of **3** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1–29 h. [b]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c]Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated. [d]A complex mixture of unidentified products was obtained.

Table 2. Cobalt-catalysed reductive aldol reactions of 4-acryloylmorpholine (**7**) with representative ketones[a]

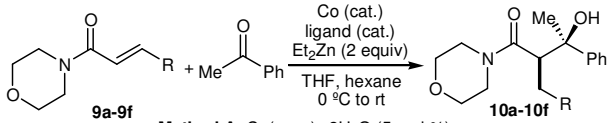


Entry	R^1	R^2	Product(s)	dr[b]	Yield(s) (%)[c]
1	Me	Ph	**7a**	5.5:1	80
2	Me	2-MePh	**7b**	9:1	84
3	Me	4-MeOPh	**7c**	6.5:1	85
4	Me	2-naphthyl	**7d**, **8d**	4.5:1	82 (17)
5	Me	2-furyl	**7e**, **8e**	3:1	72 (22)
6	Me	*i*-Pr	**7f**, **8f**	1:1	33 (31)
7	Me	*i*-Bu	**7g**, **8g**	1:1	35 (36)
8	Et	Ph	**7h**	6:1	75
9	Ph	Ph	**7i**	n/a	62

[a]Reactions were conducted using 1.0 mmol of **6** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 3–7 h. [b]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c]Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

this particular ketone leads to deleterious side-reactions under these conditions. Other aromatic ketones, such as those containing naphthyl or furyl substituents (Table 1, entries 8–9 and Table 2, entries 4–5), propiophenone (Table 2, entry 8) and benzophenone (Table 2, entry 9) were also tolerated. Aliphatic ketones also proved to be viable substrates in these reactions (Table 2, entries 6–7). However, no diastereoselection was observed in these cases, and both diastereomeric products were isolated in comparable yields. The reaction of ethyl pyruvate with **3** provided only a complex mixture (Table 1, entry 10). Next, using acetophenone as the electrophile, a study of the effect of substitution at the β-carbon of the α,β-unsaturated amide component was carried out (Table 3). These reactions proceeded to give aldol products **10a**–**10f** with ≥9:1 dr, demonstrating the beneficial effect of a β-substituent on diastereoselectivity. Amides containing linear or branched alkyl groups at the β-position were tolerated (entries 1–3), but the use of an alternative precatalyst combination of $CoCl_2$ with the electron-rich monophosphine Cy_2PPh was required for complete conversions.[xcixa] Under standard conditions, substrates containing aromatic (entries 4–5) or heteroaromatic (entry 6) groups also provided good results.

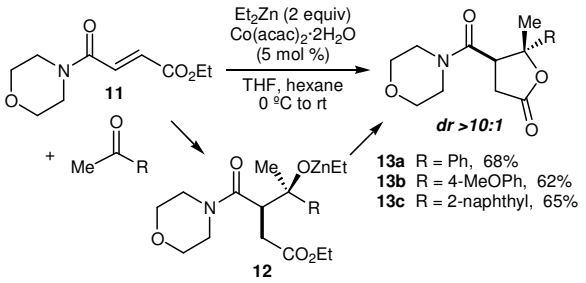
Table 3. Cobalt-catalysed reductive aldol reactions of acetophenone with representative α,β-unsaturated morpholine amides[a]



Entry	Method	R	Substrate	Product	dr[b]	Yield (%)[c]
1	B	Me	**9a**	**10a**	>19:1	76
2	B	*i*-Bu	**9b**	**10b**	>19:1	85
3	B	CH_2CH_2Ph	**9c**	**10c**	16:1	81[d]
4	A	Ph	**9d**	**10d**	>19:1	71
5	A	2-naphthyl	**9e**	**10e**	10:1	74
6	A	2-furyl	**9f**	**10f**	9:1	84

[a]Reactions were conducted using 1.0 mmol of **9a**–**9f** and 1.1 mmol of acetophenone in THF (10 mL) and hexane (2 mL) for 2–6 h. [b]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c]Isolated yield of major diastereomer. [d]Yield of a 16:1 inseparable mixture of diastereomers.

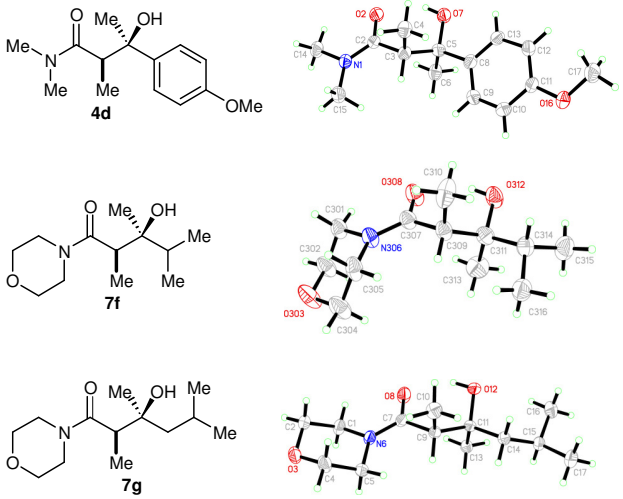
Although α,β-unsaturated esters such as *tert*-butyl acrylate and methyl cinnamate also underwent successful reaction with acetophenone under these conditions, they provided the products as *ca.* 1:1 mixtures of diastereoisomers. Therefore, the reaction of substrate **11** was of interest, since there is the potential to generate products of reductive aldol coupling α- to the ester, as well as α- to the amide. In the event, reaction of **11** with a range of methyl ketones provided only lactones **13a**–**13c**, formed through cyclisation of the intermediate zinc alkoxides **12** onto the pendant ethyl ester, in 62–68% yield (Scheme 1). These experiments demonstrate the high chemoselectivity for generation of amide enolates rather than ester enolates under these conditions.



Scheme 1. Formation of lactones **13a**–**13c** via reductive aldol coupling of **11**.

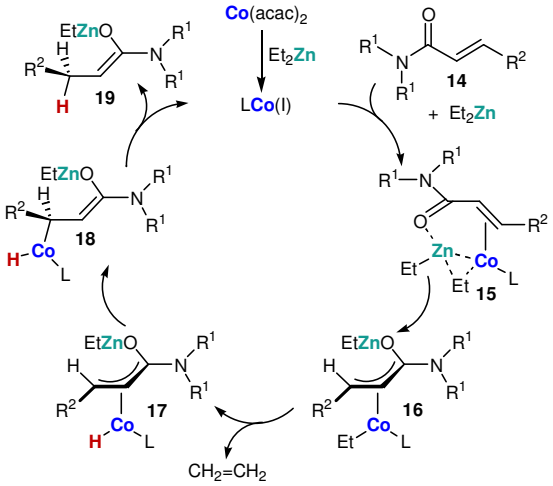
Attempts to extend the scope of these reactions by using α-substituted α,β-unsaturated amides such as 4-methacryloyl morpholine were unsuccessful, providing only complex mixtures.

X-ray crystal structures of aldol products **4d**, **7f**, and **7g** allowed determination of their relative stereochemistry[civ] (Scheme 2), and the relative configurations of the remaining products in Tables 1–3 and Scheme 1 were assigned by analogy.



Scheme 2. X-ray structures of **4d**, **7f**, and **7g**.

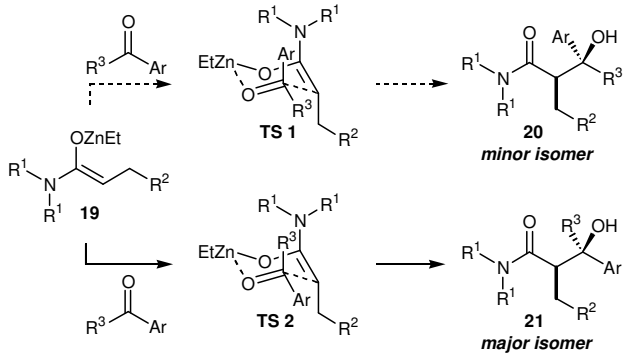
Our current working model for the mechanism of these reactions[cv] is presented in Scheme 3, and involves the participation of π-allylcobalt species. Seminal work by MacKenzie and co-workers,[cvi] along with important contributions by Ogoshi, Kurosawa, and co-workers[cvii] have described the oxidative addition of low-valent transition-metals to α,β-unsaturated carbonyl compounds in the presence of a suitable Lewis acid to form π-allylmetal complexes. In addition, strong evidence has been provided that such π-allylmetal species are intermediates in Pd-catalysed conjugate addition reactions of organometallic reagents[cviia] and disilanes.[cviib]



Scheme 3. Possible catalytic cycle.

Given this precedent, we believe that treatment of $Co(acac)_2$ with Et_2Zn leads to the formation of a cobalt (I) species that, with the assistance of additional Et_2Zn, binds to the substrate **14**, as in **15**. The presence of a three-center–two-electron bridging interaction between cobalt, zinc, and an ethyl ligand in **15** has precedent in the work of a detailed study by Montgomery and co-workers in related nickel-catalysed reactions,[cviii] and has been observed crystallographically for cobalt[cix] and nickel[cx] complexes involving Grignard[cix,cxa] and organoaluminium[cxb] reagents. From **15**, oxidative addition of Co(I) into the α,β-unsaturated amide along with transmetalation of an ethyl group from zinc to cobalt would then generate π-allylcobalt(III) species **16**, that can then undergo β-hydride elimination to give cobalt hydride **17**. η^3-η^1 Isomerisation would then provide **18**, which upon reductive elimination would give *Z*-zinc enolate **19** that undergoes aldol reaction with the ketone, along with regeneration of Co(I). In this model, the regiochemical outcome of conjugate reduction of **11** (Scheme 1) may be explained by preferential binding of Et_2Zn/Co at the amide carbonyl rather than the ester carbonyl, due to the greater Lewis basicity of the amide.

The diastereochemical outcomes of these reactions[ciii,civ] may be explained via the intervention of a chelated chair-like Zimmerman–Traxler transition state[cxi] in which the larger aromatic substituent of the ketone prefers to reside in a less sterically hindered pseudoequatorial position (as in **TS 2**) (Scheme 4), rather than in a pseudoaxial position (as in **TS 1**). The absence of diastereoselectivity with aliphatic ketones (Table 1, entries 6–7) is due presumably to reduced differences in size between the two substituents attached to the carbonyl group.



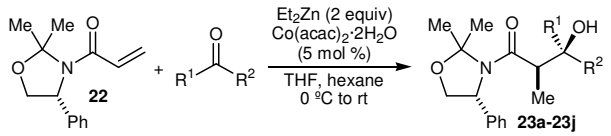
Scheme 4. Model for stereochemical outcome.

Having demonstrated the general scope of these intermolecular reductive aldol reactions, we sought to develop an asymmetric variant of the process. Examination of the literature reveals that compared with the large body of work pertaining to asymmetric aldol reactions using aldehydes as the electrophiles,[cxii] there are far fewer examples using ketones.[cxiii,cxiv,cxv] Factors responsible for this paucity include the attenuated reactivity of ketones compared with aldehydes, problems with retroaldolisation, and smaller differences in steric properties between the two substituents attached to the ketone carbonyl. The latter feature is often manifested in low levels of diastereoselectivity (such as in Table 1, entries 6–7) and enantiofacial discrimination. Although a number of approaches to address these challenges have been documented,[cxiii–cxv] there remains room for improvement, since existing procedures often display suboptimal selectivities or narrow substrate scope. Therefore, the development of new, complementary methods for conducting asymmetric ketone aldol reactions continues to be a valuable endeavour.

The prospects of developing a catalytic asymmetric variant of the reactions described herein through the use of a suitable chiral cobalt–ligand complex was deemed unpromising, since according to our mechanistic hypotheses (Schemes 3–4), cobalt is not a participant in the aldol reaction. Indeed, initial trials using substoichiometric quantities of various chiral ligands did not give rise to any enantioselection.[cxvi] Therefore, we turned to a chiral auxiliary strategy, and a number of potential candidates were screened for their ability to give both high reaction efficiencies and high levels of enolate diastereofacial selectivity. Although *N*-alkenoyloxazolidinones seemed an obvious first choice,[cxiia] these substrates did not provide aldol products under our conditions. Fortunately, *N*-acryloyloxazolidine **22**[cxvii] was found to meet our desired criteria, reacting with acetophenone to afford aldol product **23a** in 73% yield and with 11:1 diastereoselectivity [major isomer:Σ(other isomers)][cxviii] (Table 4, entry 1). Further exploration of ketone scope revealed that acetophenone derivatives containing substituents of varying electronic properties were tolerated, giving aldol products in 58-76% yield and with up to 12:1 diastereoselectivity (entries 2–6).[cxviii] Acryloyloxazolidine **22** also underwent reaction with ketones bearing naphthyl (entries 7 and 9),

heteroaromatic (entry 8) and ethyl substituents (entry 10). Aliphatic ketones proved to be less suitable substrates in this reaction, providing what appeared to be mixtures of all four possible diastereoisomers (entry 9).

Table 4. Cobalt-catalysed reductive aldol reactions of *N*-acryloyloxazolidine **22** with representative ketones[a]

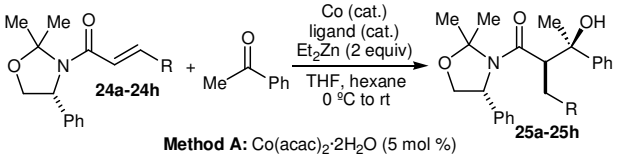


Entry	R^1	R^2	Product	dr[b,c]	Yield (%)[d]
1	Me	Ph	**23a**	11:1	73
2	Me	4-MePh	**23b**	9:1	76
3	Me	3-MePh	**23c**	12:1	72
4	Me	4-MeOPh	**23d**	8.5:1	72
5	Me	4-BrPh	**23e**	12:1	63
6	Me	3-ClPh	**23f**	7:1	58
7	Me	2-naphthyl	**23g**	13:1	75
8	Me	2-thienyl	**23h**	6:1	61
9	Me	*t*-Bu	**23i**	n/a	0[e]
10	Et	6′-MeO-2-naphthyl	**23j**	6:1	59

[a]Reactions were conducted using 1.0 mmol of **22** and 1.1 mmol of ketone in THF (5 mL) and hexane (2 mL) for 3–17 h. [b]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c]dr = (major isomer):Σ(other isomers). [d]Isolated yield of major diastereomer. [e]A complex mixture was obtained.

Table 5 presents the results of reaction of a range of *N*-alkenoyloxazolidines **24a**–**24h** with acetophenone. As seen previously in Table 3, these examples illustrate that substitution at the acrylamide has a beneficial effect on reaction diastereoselectivity (≥15:1). In addition, the

Table 5. Cobalt-catalysed reductive aldol reactions of acetophenone with representative *N*-alkenoyloxazolidines[a]



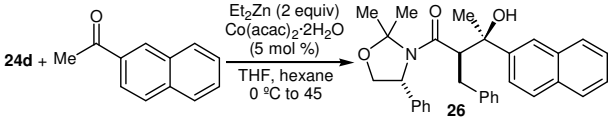
Method A: $Co(acac)_2·2H_2O$ (5 mol %)
Method B: $CoCl_2$ (5 mol %), Cy_2PPh (5.5 mol %)

Entry	Method	R	Substrate	Product	dr[b,c]	Yield (%)[d]
1	B	Me	**24a**	**25a**	16:1	82
2	B	*i*-Pr	**24b**	**25b**	15:1	79
3	B	CH_2CH_2Ph	**24c**	**25c**	15:1	80
4	A	Ph	**24d**	**25d**	>19:1	86
5	A	4-MeOPh	**24e**	**25e**	>19:1	86
6	A	4-ClPh	**24f**	**25f**	>19:1	84
7	A	2-naphthyl	**24g**	**25g**	>19:1	90
8	A	2-furyl	**24h**	**25h**	>19:1	83

[a]Reactions were conducted using 0.5 mmol of **24a**–**24h** and 0.55 mmol of acetophenone in THF (2.5 mL) and hexane (1 mL) for 4–6 h. [b]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c]dr = (major isomer):Σ(other isomers). [d]Isolated yield of major diastereomer.

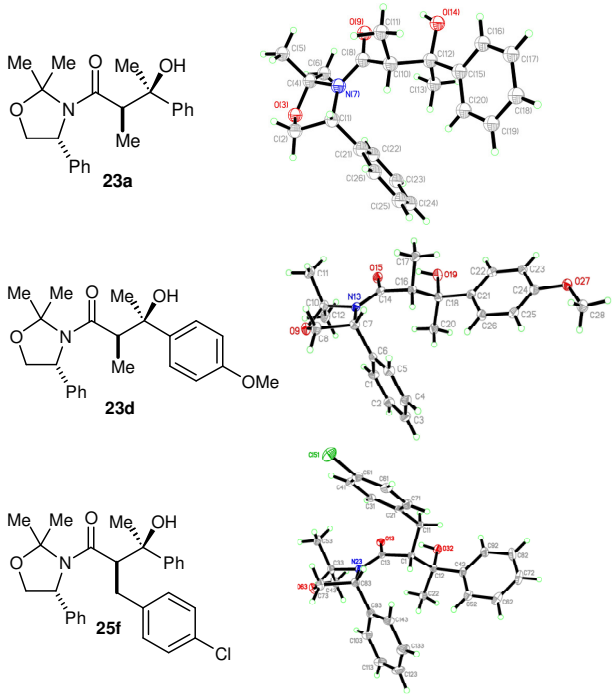
reactions of **24a**–**24h** were cleaner than those of *N*-acryloyloxazolidine **22**, which resulted in higher isolated yields of products. Once again, the combination of $CoCl_2$ and Cy_2PPh[xcixa] was required for complete conversions when acrylamides **24a**–**24c** containing alkyl substitution were employed (entries 1–3). Aromatic- and heteroaromatic-substituted *N*-alkenoyloxazolidines **24d**–**24h** were the best substrates in these reactions, affording aldol products in 83–90% yield as one observable diastereomer (>19:1 by ^{1}H NMR analysis) (entries 4–8).

The yields and diastereoselectivities of these reactions are maintained on increasing the scale. For example, reaction of cinnamoyl-substituted oxazolidine **24d** with 2-acetonaphthone to give **26** on 0.5 mmol and 5 mmol scales gave comparable results (eq 2).



0.5 mmol scale 91% yield, >19:1 dr (2)
5 mmol scale 90% yield, >19:1 dr

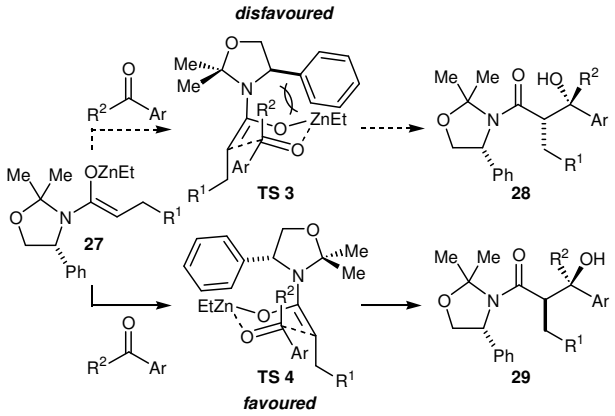
The stereochemistries of **23a**, **23d**, and **25f** were determined by X-ray crystallography (Scheme 5),[cxix] and the stereochemistries of the remaining aldol products in Tables 4–5, and of **26** were assigned by analogy.



Scheme 5. X-ray structures of **23a**, **23d**, and **25f**.

To explain the sense of asymmetric induction observed in these reactions, we suggest that in the Zimmerman–Traxler transition state,[cxi] the geminal dimethyl groups of the oxazolidine are oriented *anti* to the enolate oxygen to minimise unfavourable nonbonding interactions (Scheme 6). Inspection of alternative transition states **TS 3** and **TS 4** reveals that the oxazolidine phenyl substituent suffers

fewer nonbonding interactions in **TS 4**, which leads to the observed stereochemistry of the major isomer **29**.



Scheme 6. Model for asymmetric induction.

Obviously, the utility of this chiral auxiliary methodology is apparent only if the oxazolidine may be cleaved cleanly from the aldol products in high yield. On the basis of literature precedent,[cxviib] we expected this task to be straightforward. However, all of our efforts have been frustrated by the low reactivity of the amide carbonyl of these compounds, presumably due to high steric shielding. For example, attempted reductive cleavage of the oxazolidine from **23a** using hydride reagents such as $LiBEt_3H$,[cxviib] LAB,[cxx] $LiAlH_4$, or DIBAL resulted in no reaction at low-to-moderate temperatures, or retroaldol fragmentation at elevated temperatures. The TBS ether of **23a** was also inert to these reagents, even under forcing conditions. Various efforts to protect the tertiary alcohol of the aldol products with other protecting groups such as MEM or benzyl ethers were unsuccessful, again presumably due to high steric hindrance. Finally, attempts at acidic hydrolysis[cxxi] of the oxazolidine of **23a**, or efforts to remove the isopropylidine group[cxviib] under various Brønsted or Lewis acidic conditions, were complicated by elimination of the tertiary alcohol to provide β,γ-unsaturated compounds.

3. Conclusion

Cobalt-catalysed conjugate reduction of α,β-unsaturated amides using diethylzinc as the stoichiometric reductant generates zinc enolates that participate in efficient aldol couplings with ketones, providing tertiary β-hydroxycarbonyl products. A wide range of substitution at the β-carbon of the α,β-unsaturated amide is tolerated, and best results in terms of diastereoselectivity are obtained with aromatic ketones such as acetophenone derivatives. Although aliphatic ketones were found to undergo the reductive aldol reaction, their reactions exhibit no diastereoselectivity.

Although a readily accessible *N*-phenylglycinol-derived chiral auxiliary was found to impart high levels of asymmetric induction in these reactions, all attempts to cleave the oxazolidine from the products have been unsuccessful due to the sterically hindered nature of the products, coupled with the presence of relatively sensitive tertiary benzylic alcohols. However, this study has defined structural features for an auxiliary that gives high levels of asymmetric induction, and provides useful information that might aid in the design of improved auxiliaries in future.

4. Experimental Section

4.1. General

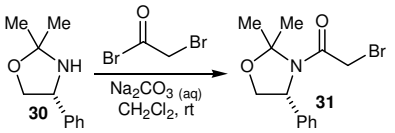
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontoursolventsystems.com. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Commercially available $CoCl_2$ was dried by heating under vacuum until it turned from purple to blue. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. ^{31}P NMR spectra were recorded on a Bruker ARX250 (101.2 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of H_3PO_4. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

Products **4**–**13c** in Tables 1–3 and Scheme 1 have been reported previously.[xcixb]

4.2 Preparation of N-alkenoyloxazolidines ***22*** *and* ***24a–24h***

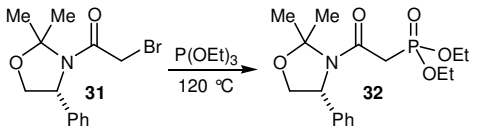
*(4R)-2,2-Dimethyl-4-phenyl-3-[(E)-propenoyl]oxazolidine (**22**)*
Prepared according to a previously reported procedure.[cxviia]

*(4R)-3-Bromoacetyl-2,2-dimethyl-4-phenyloxazolidine (**31**)*



Bromoacetyl bromide (7.2 mL, 82.5 mmol) was added in one portion to a vigorously stirred mixture of the oxazolidine **30**[cxviia] (9.75 g, 55.0 mmol) in CH_2Cl_2 (55 mL) and saturated aqueous Na_2CO_3 solution (220 mL), and the mixture was stirred at room temperature for 4 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/hexane) gave the *bromoamide* **31** (10.14 g, 62%) as a light brown solid. m.p. 90-92 °C; $[\alpha]_D^{21}$ –190 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2985, 1660 (C=O), 1400, 1379, 1255, 1237, 1137, 1066, 844, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40-7.36 (2H, m, Ar*H*), 7.34-7.29 (3H, m, Ar*H*), 5.07 (1H, dd, *J* = 6.6, 2.7 Hz, CH_2O), 4.39 (1H, dd, *J* = 9.0, 6.6 Hz, C*H*N), 3.91 (1H, dd, *J* = 9.0, 2.7 Hz, CH_2O), 3.55 (1H, d, *J* = 11.0 Hz, CH_2Br), 3.44 (1H, d, *J* = 11.0 Hz, CH_2Br), 1.86 (3H, s, C(CH_3)$_2$), 1.63 (3H, s, C(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.7 (C), 140.3 (C), 129.0 (2 x CH), 128.1 (CH), 125.6 (2 x CH), 96.4 (C), 71.2 (CH_2), 61.0 (CH), 29.2 (CH_2), 25.0 (CH_3), 22.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{13}H_{17}{}^{79}BrNO_2$ $[M+H]^+$: 298.0438, found: 298.0444.

*(4R)-3-Diethylphosphonacetyl-2,2-dimethyl-4-phenyloxazolidine (**32**)*



A stirred solution of the bromoamide **31** (10.40 g, 35.0 mmol) in triethyl phosphite (70 mL) was heated at 120 °C for 2 h. Excess triethyl phosphite was removed by distillation to leave the *phosphonate* **32** (11.82 g, 95%) as a yellow oil. $[\alpha]_D^{21}$ –114 (*c* 1.00, $CHCl_3$); IR (film) 2985, 1654 (C=O), 1419, 1392, 1365, 1254, 1052, 1025, 974, 704 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.36 (2H, m, Ar*H*), 7.34-7.29 (3H, m, Ar*H*), 5.39 (1H, dd, *J* = 6.5, 1.9 Hz, OCH_2CHN), 4.40 (1H, dd, *J* = 8.9, 6.5 Hz, C*H*N), 4.22-4.05 (4H, m, P(OCH_2CH$_3$)$_2$), 3.91 (1H, dd, *J* = 8.9, 1.9 Hz, OCH_2CHN), 2.83 (1H, dd, *J* = 20.3, 14.2 Hz, CH_2P), 2.61 (1H, dd, *J* = 23.5, 14.2 Hz, CH_2P), 1.86 (3H, s, C(CH_3)$_2$), 1.65 (3H, s, C(CH_3)$_2$), 1.37-1.33 (3H, m, CH$_2$CH_3), 1.32-1.28 (3H, m, CH$_2$CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.2 (C, d, J_P = 5.3 Hz), 140.8 (C), 128.7 (2 x CH), 127.6 (CH), 125.8 (2 x CH), 95.9 (C), 70.8 (CH_2), 62.5 (CH_2, d, J_P = 6.4 Hz), 61.8 (CH_2, d, J_P = 6.4 Hz), 60.9 (CH), 35.9 (CH_2, d, J_P = 130.8 Hz), 25.0 (CH_3), 22.3 (CH_3), 16.0 (CH_3, d, J_P = 5.8 Hz), 15.9 (CH_3, d, J_P = 5.7 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 21.7; HRMS (FAB) Exact mass calcd for $C_{17}H_{27}NO_5P$ $[M+H]^+$: 356.1622, found: 356.1627.

Wadsworth–Emmons reactions: General procedure A

A solution of the phosphonate **32** (1.42 g, 4.00 mmol) in THF (15 mL) was added *via* cannula to a suspension of NaH (60% dispersion in mineral oil, 160 mg, 4.00 mmol) in THF (15 mL) over 3 min at 0 °C. The mixture was then stirred at room temperature for 30 min before being cooled to 0 °C. The appropriate aldehyde (1 equiv) was added dropwise or portionwise over 5 min, and the mixture was then stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (20 mL), followed by the addition of Et_2O (20 mL). The organic layer was separated and washed with NH_4Cl solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) afforded the *N*-alkenoyloxazolidine.

*(4R)-3-[(E)-But-2-enoyl]-2,2-dimethyl-4-phenyloxazolidine (**24a**)*
Prepared according to a previously reported procedure.[cxxi]

*(4R)-2,2-Dimethyl-3-[(E)-4-methylpent-2-enoyl]-4-phenyloxazolidine (**24b**)*
The title compound was prepared according to General Procedure A from isobutyraldehyde (363 µL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a yellow solid (910 mg, 83%). m.p. 90-92 °C; $[\alpha]_D^{21}$ –120 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2961, 1660 (C=O), 1455, 1396, 1361, 1256, 1068, 980, 846, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.18 (5H, m, Ar*H*), 6.72 (1H, dd, *J* = 15.1, 6.6 Hz, C*H*=CHC=O), 5.66 (1H, dd, *J* = 15.1, 1.2 Hz, CH=C*H*C=O), 4.95 (1H, dd, *J* = 6.6, 2.8 Hz, CH_2O), 4.31 (1H, dd, *J* = 8.9, 6.6 Hz, C*H*N), 3.84 (1H, dd, *J* = 8.9, 2.8 Hz, CH_2O), 2.21-2.11 (1H, m, C*H*(CH$_3$)$_2$), 1.82 (3H, s, C(CH_3)$_2$), 1.63 (3H, s, C(CH_3)$_2$), 0.79 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 0.76 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 151.7 (CH), 141.4 (C), 128.5 (2 x CH), 127.3 (CH), 125.7 (2 x CH), 120.1 (CH), 95.7 (C), 71.0 (CH_2), 61.0 (CH), 30.3 (CH), 25.0 (CH_3), 23.2 (CH_3), 20.9 (2 x CH_3); HRMS (FAB) Exact mass calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found: 274.1807.

*(4R)-2,2-Dimethyl-3-[(E)-5-phenylpent-2-enoyl]-4-phenyloxazolidine (**24c**)*
The title compound was prepared according to General Procedure A from hydrocinnamaldehyde (527 µL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a yellow oil (1.12 g, 83%). $[\alpha]_D^{21}$ –98.0 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2983, 1660 (C=O), 1495, 1375, 1252, 1141, 1068, 848, 735, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40-7.16 (8H, m, Ar*H*), 7.08 (2H, d, *J* = 7.1 Hz, Ar*H*),

6.88 (1H, dt, *J* = 14.9, 6.9 Hz, C*H*=CHC=O), 5.79 (1H, d, *J* = 14.9 Hz, CH=C*H*C=O), 4.93 (1H, dd, *J* = 6.5, 2.4 Hz, CH_2O), 4.38 (1H, dd, *J* = 8.9, 6.5 Hz, C*H*N), 3.93 (1H, dd, *J* = 8.9, 2.4 Hz, CH_2O), 2.65-2.51 (2H, m, CH_2Ph), 2.39-2.28 (2H, m, CH_2CH$_2$Ph), 1.90 (3H, s, C(CH_3)$_2$), 1.71 (3H, s, C(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 144.8 (CH), 141.5 (C), 140.9 (C), 128.8 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.7 (CH), 125.9 (3 x CH), 123.5 (CH), 96.1 (C), 71.3 (CH_2), 61.2 (CH), 34.2 (CH_2), 33.6 (CH_2), 25.3 (CH_3), 23.4 (CH_3); HRMS (FAB) Exact mass calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1959, found: 336.1966.

*(4R)-2,2-Dimethyl-4-phenyl-3-[(E)-3-phenylpropenoyl]oxazolidine (**24d**)*
Prepared according to a previously reported procedure.[cxxi]

*(4R)-3-[(E)-3-(4-Methoxyphenyl)propenoyl)-2,2-dimethyl-4-phenyloxazolidine (**24e**)*
The title compound was prepared according to General Procedure A from *p*-anisaldehyde (489 μL, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.09 g, 76%). m.p. 125-127 °C; $[\alpha]_D^{21}$ –382 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2983, 1649 (C=O), 1511, 1422, 1395, 1304, 1242, 1173, 826, 701 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 15.3 Hz, ArC*H*=), 7.42-7.28 (5H, m, Ar*H*), 7.19 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.80 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.27 (1H, d, *J* = 15.3 Hz, ArCH=C*H*), 5.10 (1H, dd, *J* = 6.6, 2.6 Hz, CH_2O), 4.43 (1H, dd, *J* = 8.9, 6.6 Hz, C*H*N), 3.97 (1H, dd, *J* = 8.9, 2.6 Hz, CH_2O), 3.79 (3H, s, OCH_3), 1.94 (3H, s, C(CH_3)$_2$), 1.75 (3H, s, C(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 164.2 (C), 160.8 (C), 141.8 (C), 141.7 (CH), 129.3 (2 x CH), 129.0 (2 x CH), 127.9 (CH), 127.7 (C), 126.0 (2 x CH), 117.8 (CH), 114.1 (2 x CH), 96.3 (C), 71.4 (CH_2), 61.4 (CH), 55.3 (CH_3), 25.4 (CH_3), 23.5 (CH_3); HRMS (FAB) Exact mass calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found: 338.1751.

*(4R)-3-[(E)-3-(4-Chlorophenyl)propenoyl)-2,2-dimethyl-4-phenyloxazolidine (**24f**)*
The title compound was prepared according to General Procedure A from 4-chlorobenzaldehyde (562 mg, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.15 g, 84%). m.p. 117-119 °C; $[\alpha]_D^{21}$ –342 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2984, 1651 (C=O), 1568, 1492, 1393, 1301, 1245, 971, 819, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 15.4 Hz, ArC*H*=), 7.42-7.28 (5H, m, Ar*H*), 7.20 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.12 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.39 (1H, d, *J* = 15.4 Hz, ArCH=C*H*), 5.11 (1H, dd, *J* = 6.5, 2.6 Hz, CH_2O), 4.42 (1H, dd, *J* = 8.9, 6.5 Hz, C*H*N), 3.96 (1H, dd, *J* = 8.9, 2.6 Hz, CH_2O), 1.95 (3H, s, C(CH_3)$_2$), 1.75 (3H, s, C(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.2 (C), 141.4 (C), 140.2 (CH), 135.1 (C), 133.3 (C), 128.9 (2 x CH), 128.6 (4 x CH), 127.8 (CH), 125.7 (2 x CH), 120.6 (CH), 96.1 (C), 71.2 (CH_2), 61.2 (CH), 25.1 (CH_3), 23.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_{20}H_{21}{}^{35}ClNO_2$ $[M+H]^+$: 342.1256, found: 342.1261.

*(4R)-2,2-Dimethyl-3-[(E)-3-(naphthalen-2-yl)propenoyl)-4-phenyloxazolidine (**24g**)*
The title compound was prepared according to General Procedure A from 2-naphthaldehyde (625 mg, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.09 g, 76%). m.p. 131-133 °C; $[\alpha]_D^{21}$ –402 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2984, 1651 (C=O), 1401, 1362, 1255, 1239, 1068, 848, 749, 701 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.83-7.79 (3H, m, Ar*H*), 7.75-7.73 (2H, m, Ar*H*), 7.51-7.43 (6H, m, ArC*H*= and Ar*H*), 7.39-7.31 (2H, m, Ar*H*), 6.56 (1H, d, *J* = 15.3 Hz, ArCH=C*H*), 5.16 (1H, dd, *J* = 6.6, 2.8 Hz, CH_2O), 4.48 (1H, dd, *J* = 8.9, 6.6 Hz, C*H*N), 4.03 (1H, dd, *J* = 8.9, 2.8 Hz, CH_2O), 2.03 (3H, s, C(CH_3)$_2$), 1.84 (3H, s, C(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 141.8 (CH), 141.7 (C), 133.7 (C), 133.1 (C), 132.4 (C), 129.2 (CH), 129.0 (2 x CH), 128.3 (3 x CH), 127.9 (CH), 127.5 (CH), 126.8 (CH), 126.4 (CH), 125.9 (2 x CH), 123.3 (CH), 120.4 (CH), 96.3 (C), 71.3 (CH_2), 61.4 (CH), 25.3 (CH_3), 23.5 (CH_3); HRMS (FAB) Exact mass calcd for $C_{24}H_{24}NO_2$ $[M+H]^+$: 358.1802, found: 358.1807.

*(4R)-3-[(E)-3-(Furan-2-yl)propenoyl)-2,2-dimethyl-4-phenyloxazolidine (**24h**)*
The title compound was prepared according to General Procedure A from 2-furaldehyde (331 μL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a light yellow solid (1.02 g, 84%). m.p. 94-96 °C; $[\alpha]_D^{21}$ –384 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2985, 1651 (C=O), 1557, 1484, 1392, 1246, 1067, 974, 746, 701 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40-7.33 (5H, m) and 7.30-7.23 (2H, m, Ar*H*, C*H*=CHC=O, and C*H*), 6.41 (1H, d, *J* = 3.3 Hz, C*H*), 6.36-6.30 (2H, m, CH=C*H*C=O and C*H*), 5.09 (1H, dd, *J* = 6.4, 2.1 Hz, CH_2O), 4.38 (1H, dd, *J* = 8.9, 6.4 Hz, C*H*N), 3.94 (1H, dd, *J* = 8.9, 2.1 Hz, CH_2O), 1.93 (3H, s, C(CH_3)$_2$), 1.73 (3H, s, C(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.4 (C), 151.1 (C), 143.8 (CH), 141.5 (C), 128.7 (2 x CH), 128.5 (CH), 127.5 (CH), 125.7 (2 x CH), 117.4 (CH), 113.7 (CH), 111.8 (CH), 96.0 (C), 71.1 (CH_2), 60.9 (CH), 25.2 (CH_3), 23.1 (CH_3); HRMS (FAB) Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found: 298.1443.

*4.3 Cobalt-catalysed reductive aldol reactions of N-acryloyloxazolidine **22** with various ketones: General procedure B*

A solution of the *N*-alkenoyloxazolidine **22** (231 mg, 1.00 mmol), the appropriate ketone (1.10 mmol) and $Co(acac)_2{\cdot}2H_2O$ (12.9 mg, 0.05 mmol) in THF (5.0 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 2.00 mL, 2.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (30 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the aldol product.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23a**)*

The title compound was prepared according to General procedure B from acetophenone (130 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (257 mg, 73%). Recrystallisation of a CH_2Cl_2/hexane solution of **23a** at –20 °C was found to give colourless crystals suitable for X-ray diffraction. m.p. 215-217 °C; $[\alpha]_D^{21}$ –231 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3388 (OH), 2980, 2933, 2878, 1624 (C=O), 1458, 1420, 1065, 765, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53-7.48 (2H, m, Ar*H*), 7.47-7.42 (3H, m, Ar*H*); 7.23-7.12 (3H, m, Ar*H*), 6.94 (2H, app d, *J* = 7.2 Hz, Ar*H*), 5.48 (1H, br s, O*H*), 4.77 (1H, dd, *J* = 6.6, 2.2 Hz, CH_2O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 3.99 (1H, dd, *J* = 9.1, 2.2 Hz, CH_2O), 2.60 (1H, q, *J* = 7.1 Hz, CH_3CH), 1.98 (3H, s, C(CH_3)$_2$), 1.67 (3H, s, C(CH_3)$_2$), 0.99 (3H, s, CH_3COH), 0.90 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.8 (C), 142.0 (C), 129.2 (2 x CH), 128.5 (CH), 127.8 (2 x CH), 126.7 (2 x CH), 126.1 (CH), 124.5 (2 x CH), 96.3 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2064, found: 354.2064.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(4-methylphenyl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23b**)*

The title compound was prepared according to General procedure B from 4′-methylacetophenone (155 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (280 mg, 76%). m.p. 171-173 °C; $[\alpha]_D^{21}$ –249 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2985, 2932, 1621 (C=O), 1458, 1423, 1377, 1303, 1205, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.48 (2H, m, Ar*H*), 7.46-7.41 (3H, m, Ar*H*), 7.03-7.01 (2H, m, Ar*H*), 6.82 (2H, d, *J* = 7.9 Hz, Ar*H*), 5.43 (1H, s, O*H*), 4.77 (1H, dd, *J* = 6.6, 2.2 Hz, CH_2O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, CH_2O), 2.58 (1H, q, *J* = 7.1 Hz, CH_3CH), 2.29 (3H, s, ArCH_3), 1.98 (3H, s, C(CH_3)$_2$), 1.67 (3H, s, C(CH_3)$_2$), 0.98 (3H, s, CH_3COH), 0.90 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 142.9 (C), 142.0 (C), 135.6 (C), 129.1 (2 x CH), 128.5 (3 x CH), 126.7 (2 x CH), 124.4 (2 x CH), 96.2 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.7 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 20.9 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2218.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(3-methylphenyl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23c**)*

The title compound was prepared according to General procedure B from 3′-methylacetophenone (150 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (278 mg, 72%). m.p. 95-97 °C; $[\alpha]_D^{21}$ –199 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2980, 2933, 2878, 1624 (C=O), 1419, 1302, 1066, 845, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.49 (2H, m, Ar*H*), 7.47-7.43 (3H, m, Ar*H*), 7.09 (1H, t, *J* = 7.7 Hz, Ar*H*), 6.96 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.75-6.73 (2H, m, Ar*H*), 5.41 (1H, s, O*H*), 4.78 (1H, dd, *J* = 6.6, 2.2 Hz, CH_2O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, CH_2O), 2.61 (1H, q, *J* = 7.1 Hz, CH_3CH), 2.28 (3H, s, ArCH_3), 1.99 (3H, s, C(CH_3)$_2$), 1.67 (3H, s, C(CH_3)$_2$), 0.99 (3H, s, CH_3COH), 0.91 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.7 (C), 142.0 (C), 137.2 (C), 129.1 (2 x CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 126.7 (2 x CH), 125.2 (CH), 121.5 (CH), 96.1 (C), 74.6 (C), 70.9 (CH_2), 61.6 (CH), 46.6 (CH), 29.6 (CH_3), 25.5 (CH_3), 22.6 (CH_3), 21.5 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2221, found: 368.2230.

*(4R)-3-[(2R,3R)-3-Hydroxy-3-(4-methoxyphenyl)-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23d**)*

The title compound was prepared according to General procedure B from 4′-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (274 mg, 72%). Recrystallisation of an EtOAc/hexane solution of **23d** at –20 °C was found to give colourless crystals suitable for X-ray diffraction. m.p. 183-185 °C; $[\alpha]_D^{21}$ –222 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3366 (OH), 2984, 2971, 2928, 1617 (C=O), 1510, 1250, 1177, 1065, 841 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.47 (2H, m, Ar*H*), 7.46-7.42 (3H, m, Ar*H*), 6.85 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.75-6.73 (2H, m, Ar*H*), 5.44 (1H, br s, O*H*), 4.77 (1H, dd, *J* = 6.6, 2.1 Hz, CH_2O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J* = 9.1, 2.1 Hz, CH_2O), 3.76 (3H, s, OCH_3), 2.54 (1H, q, *J* = 7.1 Hz, CH_3CH), 1.98 (3H, s, C(CH_3)$_2$), 1.66 (3H, s, C(CH_3)$_2$), 0.97 (3H, s, CH_3COH), 0.90 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 157.9 (C), 142.0 (C), 138.0 (C), 129.1 (2 x CH), 128.5 (CH), 126.7 (2 x CH), 125.6 (2 x CH), 113.1 (2 x CH), 96.2 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 55.1 (CH_3), 46.8 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_4$ $[M+H]^+$: 384.2169, found: 384.2167.

*(4R)-3-[(2R,3R)-3-(4-Bromophenyl)-3-hydroxy-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23e**)*

The title compound was prepared according to General procedure B from 4′-bromoacetophenone (219 mg, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (273 mg, 63%). m.p. 132-134 °C; $[\alpha]_D^{21}$ –236 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2933, 2878, 1625 (C=O), 1457, 1411, 1066, 840, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.40 (5H, m, Ar*H*), 7.33-7.31 (2H, m, Ar*H*), 6.79 (2H, d, *J* = 8.3 Hz, Ar*H*), 5.48 (1H, s, O*H*), 4.75 (1H, dd, *J* = 6.6, 2.2 Hz,), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J* = 9.1, 2.2 Hz, CH_2O), 2.53 (1H, q, *J* = 7.1 Hz, CH_3CH), 1.97 (3H, s, C(CH_3)$_2$), 1.66 (3H, s, C(CH_3)$_2$), 0.96 (3H, s, CH_3COH), 0.88 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.9 (C), 144.9 (C), 141.9 (C), 130.8 (2 x CH), 129.2 (2 x CH), 128.6 (CH), 126.7 (2 x CH), 126.5 (2 x CH), 120.1 (C), 96.3 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 46.5 (CH), 29.4 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{27}{}^{79}BrNO_3$ $[M+H]^+$: 432.1169, found: 432.1168.

*(4R)-3-[(2R,3R)-3-(4-Bromophenyl)-3-hydroxy-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23f**)*
The title compound was prepared according to General procedure B from 3′-chloroacetophenone (143 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a colourless oil (225 mg, 58%). $[\alpha]_D^{21}$ –162 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2934, 2877, 1627 (C=O), 1419, 1205, 1066, 842, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.49 (2H, m, Ar*H*), 7.48-7.42 (3H, m, Ar*H*), 7.15-7.10 (2H, m, Ar*H*), 6.89-6.83 (2H, m, Ar*H*), 5.45 (1H, s, O*H*), 4.75 (1H, dd, *J* = 6.7, 2.2 Hz, CH_2O), 4.40 (1H, dd, *J* = 9.1, 6.7 Hz, C*H*N), 3.99 (1H, dd, *J* = 9.1, 2.2 Hz, CH_2O), 2.58 (1H, q, *J* = 7.1 Hz, CH_3CH), 1.97 (3H, s, C(CH_3)$_2$), 1.66 (3H, s, C(CH_3)$_2$), 0.93 (3H, s, CH_3COH), 0.89 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.8 (C), 148.0 (C), 141.9 (C), 133.9 (C), 129.3 (2 x CH), 129.1 (CH), 128.6 (CH), 126.7 (2 x CH), 126.3 (CH), 1245.0 (CH), 122.7 (CH), 96.2 (C), 74.4 (C), 70.9 (CH_2), 61.7 (CH), 46.5 (CH), 29.4 (CH_3), 25.5 (CH_3), 22.7 (CH_3), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{27}{}^{35}ClNO_3$ $[M+H]^+$: 388.1675, found: 388.1675.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(naphthalen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23g**)*
The title compound was prepared according to General procedure B from 2′-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (302 mg, 75%). m.p. 215-217 °C; $[\alpha]_D^{21}$ –11.2 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3410 (OH), 2980, 2933, 2878, 1624 (C=O), 1456, 1418, 1377, 1299, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.78-7.76 (2H, m, Ar*H*), 7.67 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.61-7.40 (8H, m, Ar*H*), 6.86-6.84 (1H, m, Ar*H*), 5.59 (1H, br s, O*H*), 4.80 (1H, dd, *J* = 6.6, 2.2 Hz, CH_2O), 4.42 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 4.01 (1H, dd, *J* = 9.1, 2.2 Hz, CH_2O), 2.74 (1H, q, *J* = 7.1 Hz, CH_3CH), 2.02 (3H, s, C(CH_3)$_2$), 1.69 (3H, s, C(CH_3)$_2$), 1.09 (3H, s, CH_3COH), 0.91 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 143.2 (C), 142.1 (C), 133.1 (C), 132.0 (C), 129.3 (2 x CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 126.8 (2 x CH), 125.8 (CH), 125.4 (CH), 123.5 (CH), 122.8 (CH), 96.3 (C), 74.9 (C), 71.0 (CH_2), 61.7 (CH), 46.6 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{30}NO_3$ $[M+H]^+$: 404.2220, found: 404.2221.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(thiophen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23h**)*
The title compound was prepared according to General procedure B from 2-acetylthiophene (119 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH_2Cl_2/hexane to give a white solid (220 mg, 61%). m.p. 143-145 °C; $[\alpha]_D^{21}$ –11.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3399 (OH), 2983, 2933, 2878, 1625 (C=O), 1422, 1237, 1066, 844, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50-7.39 (5H, m, Ar*H*), 7.09 (1H, dd, *J* = 5.1, 1.2 Hz, C*H*), 6.86 (1H, dd, *J* = 5.1, 3.5 Hz, C*H*), 6.35 (1H, dd, *J* = 3.5, 1.2 Hz, C*H*), 5.57 (1H, s, O*H*), 4.76 (1H, dd, *J* = 6.6, 2.1 Hz, CH_2O), 4.40 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 3.99 (1H, dd, *J* = 9.1, 2.1 Hz, CH_2O), 2.60 (1H, q, *J* = 7.1 Hz, CH_3CH), 1.96 (3H, s, C(CH_3)$_2$), 1.65 (3H, s, C(CH_3)$_2$), 1.04 (3H, d, *J* = 7.1 Hz, CH_3CH), 1.00 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.8 (C), 151.0 (C), 141.8 (C), 129.1 (2 x CH), 128.4 (CH), 126.6 (2 x CH), 126.5 (CH), 123.1 (CH), 121.0 (CH), 96.2 (C), 74.7 (C), 70.9 (CH_2), 61.5 (CH), 47.7 (CH), 30.6 (CH_3), 25.5 (CH_3), 22.6 (CH_3), 12.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_3S$ $[M+H]^+$: 360.1628, found: 360.1637.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(6-methoxynaphthalen-2-yl)pentanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23j**)*
The title compound was prepared according to General procedure B from 6′-methoxy-2′-propiononaphthone (236 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH_2Cl_2/hexane to give a white solid (265 mg, 59%). m.p. 164-166 °C; $[\alpha]_D^{21}$ –3.9 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3388 (OH), 2975, 2935, 2877, 1623 (C=O), 1417, 1266, 1173, 1067, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.58-7.45 (7H, m, Ar*H*), 7.12 (1H, dd, *J* = 8.9, 5.6 Hz, Ar*H*), 7.08 (1H, d, *J* = 2.5 Hz, Ar*H*), 5.21 (1H, s, O*H*), 4.79 (1H, dd, *J* = 6.6, 2.1 Hz, CH_2O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 3.99 (1H, dd, *J* = 9.1, 2.1 Hz, CH_2O), 3.91 (3H, s, OCH_3), 2.67 (1H, q, *J* = 7.1 Hz, CH_3CH), 2.00 (3H, s, C(CH_3)$_2$), 1.67 (3H, s, C(CH_3)$_2$), 1.65-1.55 (1H, m, CH_2CH$_3$), 0.96-0.85 (1H, m, CH_2CH$_3$), 0.90 (3H, d, *J* = 7.1 Hz, CH_3CH), 0.43 (3H, t, *J* = 7.3 Hz, CH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.5 (C), 157.3 (C), 142.1 (C), 138.6 (C), 132.9 (C), 129.5 (CH), 129.2 (2 x CH), 128.5 (CH and C), 126.7 (2 x CH), 126.2 (CH), 124.5 (CH), 123.7 (CH), 118.5 (CH), 105.3 (CH), 96.2 (C), 77.9 (C), 71.0 (CH_2), 61.6 (CH), 55.2 (CH_3), 46.8 (CH), 33.3 (CH_2), 25.7 (CH_3), 22.6 (CH_3), 12.3 (CH_3), 7.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{28}H_{34}NO_4$ $[M+H]^+$: 448.2483, found: 448.2490.

*4.4 Cobalt-catalysed reductive aldol reactions of N-alkenoyloxazolidines **24a-h** with acetophenone*

Using $Co(acac)_2{\cdot}2H_2O/Et_2Zn$: General procedure C
A solution of the appropriate *N*-alkenoyloxazolidine (0.50 mmol), acetophenone (65 μL, 0.55 mmol) and $Co(acac)_2{\cdot}2H_2O$ (6.4 mg, 0.025 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO_2 using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the aldol product.

Using $CoCl_2/Cy_2PPh/Et_2Zn$: General Procedure D
A solution of the appropriate *N*-alkenoyloxazolidine (0.50 mmol), the acetophenone (65 μL, 0.55 mmol), $CoCl_2$ (3.2 mg, 0.025 mmol) and Cy_2PPh (7.5 mg, 0.0275 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added

dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO_2 using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the aldol product.

*(4R)-3-[(2R,3R)-2-Ethyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25a**)*

The title compound was prepared according to General Procedure D from *N*-alkenoyloxazolidine **24a** (123 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (150 mg, 82%). m.p. 131-133 °C; $[\alpha]_D^{2T}$ –226 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3387 (OH), 2973, 1620 (C=O), 1457, 1408, 1308, 1133, 1067, 766, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.42 (5H, m, Ar*H*), 7.24-7.13 (3H, m, Ar*H*), 6.98 (2H, d, *J* = 7.3 Hz, Ar*H*), 5.33 (1H, s, O*H*), 4.94 (1H, dd, *J* = 6.6, 1.6 Hz, CH_2O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 4.00 (1H, dd, *J* = 9.1, 1.6 Hz, CH_2O), 2.67 (1H, dd, *J* = 10.8, 4.0 Hz, C*H*C=O), 2.01 (3H, s, C(CH_3)$_2$), 1.87-1.74 (1H, m, CH_2CH$_3$), 1.72 (3H, s, C(CH_3)$_2$), 1.21-1.10 (1H, m, CH_2CH$_3$), 0.87 (3H, t, *J* = 6.6 Hz, CH$_2$CH_3), 0.78 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.7 (C), 146.1 (C), 142.0 (C), 129.1 (2 x CH), 128.6 (CH), 127.7 (2 x CH), 127.4 (2 x CH), 126.1 (CH), 124.6 (2 x CH), 96.6 (C), 74.9 (C), 70.8 (CH$_2$), 61.9 (CH), 53.6 (CH), 29.8 (CH$_3$), 25.7 (CH$_3$), 22.6 (CH$_3$), 21.7 (CH$_2$), 12.1 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2221.

*(4R)-3-[(2R,3R)-2-iso-Butyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25b**)*

The title compound was prepared according to General Procedure D from *N*-alkenoyloxazolidine **24b** (137 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (156 mg, 79%). m.p. 195-197 °C; $[\alpha]_D^{2T}$ –182 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3346 (OH), 2954, 1612 (C=O), 1456, 1409, 1303, 1130, 1067, 768, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54-7.41 (5H, m, Ar*H*), 7.23-7.11 (3H, m, Ar*H*), 6.97 (2H, d, *J* = 7.3 Hz, Ar*H*), 5.25 (1H, s, O*H*), 4.90 (1H, dd, *J* = 6.6, 1.6 Hz, CH_2O), 4.41 (1H, dd, *J* = 9.1, 6.6 Hz, C*H*N), 4.00 (1H, dd, *J* = 9.1, 1.6 Hz, CH_2O), 2.74 (1H, dd, *J* = 10.1, 3.2 Hz, C*H*C=O), 2.01 (3H, s, C(CH_3)$_2$), 1.76-1.67 (1H, m, CH_2CH(CH$_3$)$_2$), 1.61 (3H, s, C(CH_3)$_2$), 1.32-1.20 (1H, m, C*H*(CH$_3$)$_2$), 1.04 (1H, ddd, *J* = 14.1, 9.5, 3.2 Hz, CH_2CH(CH$_3$)$_2$), 0.82 (3H, d, *J* = 6.5 Hz, CH(CH_3)$_2$), 0.77 (3H, s, CH_3COH), 0.75 (3H, d, *J* = 6.5 Hz, CH(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 146.1 (C), 141.9 (C), 129.2 (2 x CH), 128.6 (CH), 127.7 (2 x CH), 127.2 (2 x CH), 126.1 (CH), 124.5 (2 x CH), 96.6 (C), 75.3 (C), 70.9 (CH$_2$), 61.6 (CH), 50.6 (CH), 38.5 (CH$_2$), 30.2 (CH$_3$), 26.0 (CH), 25.6 (CH$_3$), 23.9 (CH$_3$), 22.7 (CH$_3$), 22.6 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{25}H_{34}NO_3$ $[M+H]^+$: 396.2533, found: 396.2534.

*(4R)-3-[(2R,3R)-3-Hydroxy-3-phenylbutanoyl-2-(3-phenylpropyl)]-2,2-dimethyl-4-phenyloxazolidine (**25c**)*

The title compound was prepared according to General Procedure D from *N*-alkenoyloxazolidine **24c** (168 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (182 mg, 80%). m.p. 130-132 °C; $[\alpha]_D^{2T}$ –190 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 3028, 1619 (C=O), 1427, 1397, 1066, 1053, 837, 740, 706 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.59-7.48 (5H, m, Ar*H*), 7.34-7.22 (6H, m, Ar*H*), 7.11 (2H, d, *J* = 7.2 Hz, Ar*H*), 7.06 (2H, d, *J* = 7.2 Hz, Ar*H*), 5.41 (1H, s, O*H*), 4.86 (1H, dd, *J* = 6.5, 1.5 Hz, CH_2O), 4.37 (1H, dd, *J* = 9.1, 6.5 Hz, C*H*N), 4.01 (1H, dd, *J* = 9.1, 1.5 Hz, CH_2O), 2.77 (1H, dd, *J* = 9.9, 4.0 Hz, C*H*C=O), 2.52 (2H, t, *J* = 7.2 Hz, CH_2Ar), 2.07 (3H, s, C(CH_3)$_2$), 1.94-1.82 (1H, m, CHCH_2CH$_2$), 1.76 (3H, s, C(CH_3)$_2$), 1.69-1.56 (1H, m, CHCH_2CH$_2$), 1.50-1.31 (2H, m, CH$_2$CH_2CH$_2$), 0.89 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.6 (C), 146.0 (C), 141.9 (C), 141.8 (C), 129.1 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 128.1 (2 x CH), 127.7 (2 x CH), 127.2 (2 x CH), 126.1 (CH), 125.7 (CH), 124.6 (2 x CH), 96.5 (C), 74.8 (C), 70.8 (CH$_2$), 61.7 (CH), 52.3 (CH), 36.2 (CH$_2$), 29.8 (CH$_3$ and CH$_2$), 28.4 (CH$_2$), 25.6 (CH$_3$), 22.5 (CH$_3$); HRMS (FAB) Exact mass calcd for $C_{30}H_{36}NO_3$ $[M+H]^+$: 458.2690, found: 458.2687.

(4R)-3-[(2R,3R)-2-Benzyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (***25d***)

The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **24d** (154 mg, 0.50 mmol) for a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (184 mg, 86%). m.p. 139-141 °C; $[\alpha]_D^{2T}$ –286 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3387 (OH), 3026, 1620 (C=O), 1455, 1421, 1301, 1249, 1065, 843, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.41 (3H, m, Ar*H*), 7.39-7.24 (8H, m, Ar*H*), 7.14-7.09 (4H, m, Ar*H*), 5.56 (1H, s, O*H*), 3.68 (1H, dd, *J* = 9.0, 6.4 Hz, C*H*N), 3.62 (1H, dd, *J* = 9.0, 1.3 Hz, CH_2O), 3.35 (1H, app d, *J* = 5.4 Hz, CH_2O), 3.05 (1H, app t, *J* = 12.5 Hz, C*H*C=O), 2.90 (1H, dd, *J* = 11.9, 2.6 Hz, CH_2Ph), 2.43 (1H, dd, *J* = 13.0, 2.6 Hz, CH_2Ph), 1.98 (3H, s, C(CH_3)$_2$), 1.65 (3H, s, C(CH_3)$_2$), 0.92 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 146.0 (C), 142.1 (C), 140.0 (C), 129.1 (2 x CH), 128.9 (2 x CH), 128.5 (2 x CH), 128.3 (CH), 127.9 (2 x CH), 127.0 (2 x CH), 126.7 (CH), 126.3 (CH), 124.5 (2 x CH), 96.3 (C), 75.3 (C), 70.4 (CH$_2$), 60.5 (CH), 55.7 (CH), 34.9 (CH$_2$), 29.7 (CH$_3$), 25.5 (CH$_3$), 22.1 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{28}H_{32}NO_3$ $[M+H]^+$: 430.2377, found: 430.2382.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-(4-methoxybenzyl)-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25e**)*

The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **24e** (169 mg, 0.50 mmol) for a reaction time of 6 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (198 mg, 86%). m.p. 115-117 °C; $[\alpha]_D^{2T}$ –304 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3386 (OH), 3027, 1618 (C=O), 1511, 1456, 1418, 1109, 1066, 768, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.41 (3H, m, Ar*H*), 7.36-7.22 (5H, m, Ar*H*), 7.07-7.05 (2H, m, Ar*H*), 7.02 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.90 (2H, d, *J* = 8.6 Hz, Ar*H*), 5.56 (1H, s, O*H*), 3.83 (3H, s, OCH_3), 3.75 (1H, dd, *J* = 9.0, 6.5 Hz, C*H*N), 3.65 (1H, dd, *J* = 9.0, 1.1 Hz, CH_2O),

3.47 (1H, app d, J = 5.8 Hz, CH_2O), 3.00 (1H, dd, J = 13.1, 11.9 Hz, CHC=O), 2.88 (1H, dd, J = 11.9, 2.4 Hz, CH_2Ar), 2.36 (1H, dd, J = 13.1, 2.4 Hz, CH_2Ar), 1.98 (3H, s, C(CH_3)$_2$), 1.66 (3H, s, C(CH_3)$_2$), 0.91 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.0 (C), 158.4 (C), 146.0 (C), 142.1 (C), 131.9 (C), 130.0 (2 x CH), 128.9 (2 x CH), 128.3 (CH), 127.9 (2 x CH), 127.0 (2 x CH), 126.2 (CH), 124.4 (2 x CH), 113.8 (2 x CH), 96.2 (C), 75.2 (C), 70.4 (CH_2), 60.6 (CH), 55.7 (CH), 55.2 (CH_3), 34.0 (CH_2), 29.7 (CH_3), 25.4 (CH_3), 22.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{29}H_{34}NO_4$ $[M+H]^+$: 460.2482, found: 460.2482.

*(4R)-3-[(2R,3R)-2-(4-Chlorobenzyl)-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25f**)*
The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **24f** (171 mg, 0.50 mmol) for a reaction time of 6 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (194 mg, 84%). Slow evaporation of a $CDCl_3$ solution of **25f** was found to give colourless crystals suitable for X-ray diffraction. m.p. 139-140 °C; $[\alpha]_D^{21}$ –304 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 3027, 1627 (C=O), 1493, 1423, 1313, 1296, 910, 767, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.53-7.43 (3H, m, ArH), 7.36-7.23 (7H, m, ArH), 7.04 (4H, dm, J = 8.4 Hz, ArH), 5.46 (1H, s, OH), 3.76 (1H, dd, J = 9.1, 6.5 Hz, CHN), 3.68 (1H, dd, J = 9.1, 1.3 Hz, CH_2O), 3.48 (1H, dd, J = 6.5, 1.3 Hz, CH_2O), 3.00 (1H, dd, J = 13.1, 11.9 Hz, CHC=O), 2.88 (1H, dd, J = 11.9, 2.7 Hz, CH_2Ar), 2.37 (1H, dd, J = 13.1, 2.7 Hz, CH_2Ar), 1.98 (3H, s, C(CH_3)$_2$), 1.62 (3H, s, C(CH_3)$_2$), 0.89 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 145.8 (C), 141.9 (C), 138.5 (C), 132.5 (C), 130.5 (2 x CH), 129.0 (2 x CH), 128.5 (4 x CH), 128.0 (2 x CH), 127.1 (2 x CH), 126.4 (CH), 124.5 (CH), 96.4 (C), 75.2 (C), 70.4 (CH_2), 60.8 (CH), 55.4 (CH), 34.2 (CH_2), 29.6 (CH_3), 25.5 (CH_3), 22.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{28}H_{31}{}^{35}ClNO_3$ $[M+H]^+$: 464.1987, found: 464.1990.

*(4R)-3-[(2R,3R)-3-Hydroxy-2-(naphthalen-2-ylmethyl)-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25g**)*
The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **24g** (179 mg, 0.50 mmol) for a reaction time of 16 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (216 mg, 90%). m.p. 136-138 °C; $[\alpha]_D^{21}$ –358 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3389 (OH), 3026, 1620 (C=O), 1420, 1302, 1249, 1067, 908, 733, 703 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94-7.88 (2H, m, ArH), 7.85 (2H, d, J = 8.6 Hz, ArH), 7.61-7.51 (5H, m, ArH), 7.38-7.29 (5H, m, ArH), 7.14-7.11 (2H, m, ArH), 6.99 (1H, br s, ArH), 5.72 (1H, s, OH), 3.73 (1H, dd, J = 9.0, 6.4 Hz, CHN), 3.66 (1H, dd, J = 9.0, 1.1 Hz, CH_2O), 3.38 (1H, app d, J = 5.9 Hz, CH_2O), 3.15 (1H, dd, J = 12.6, 12.0 Hz, CHC=O), 3.06 (1H, dd, J = 12.0, 1.8 Hz, CH_2Ar), 2.48 (1H, dd, J = 12.6, 1.8 Hz, CH_2Ar), 2.05 (3H, s, C(CH_3)$_2$), 1.71 (3H, s, C(CH_3)$_2$), 1.07 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 143.2 (C), 142.2 (C), 139.9 (C), 133.1 (C), 132.1 (C), 129.1 (2 x CH), 129.0 (2 x CH), 128.4 (3 x CH), 128.1 (CH), 127.6 (CH), 127.3 (CH), 127.1 (2 x CH), 126.7 (CH), 125.9 (CH), 125.5 (CH), 123.6 (CH), 122.7 (CH), 96.3 (C), 75.5 (C), 70.4 (CH_2), 60.5 (CH), 55.5 (CH), 35.0 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{32}H_{34}NO_3$ $[M+H]^+$: 480.2533, found: 480.2539.

*(4R)-3-[(2R,3R)-2-(Furan-2-ylmethyl)-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25h**)*
The title compound was prepared according to General Procedure C from *N*-alkenoyloxazolidine **24h** (149 mg, 0.50 mmol) for a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (174 mg, 83%). m.p. 96-98 °C; $[\alpha]_D^{21}$ –298 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3378 (OH), 3028, 1622 (C=O), 1456, 1378, 1066, 1013, 914, 767, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.55-7.51 (2H, m, ArH), 7.47-7.43 (4H, m, ArH), 7.33-7.29 (2H, m, ArH), 7.25-7.21 (1H, m, ArH) 7.09-7.07 (2H, m, ArH, CH), 6.38 (1H, dd, J = 3.2, 1.9 Hz, CH), 6.03 (1H, d, J = 3.2 Hz, CH), 5.56 (1H, s, OH), 4.00 (1H, dd, J = 8.8, 6.5 Hz, CH_2N), 3.87 (1H, dd, J = 6.5, 1.2 Hz, CH_2O), 3.82 (1H, dd, J = 8.8, 1.2 Hz, CH_2O), 3.13 (1H, dd, J = 13.1, 11.8 Hz, CHC=O), 3.07 (1H, dd, J = 11.8, 1.7 Hz, CH_2CHC=O), 2.39 (1H, dd, J = 13.1, 1.7 Hz, CH_2CH), 1.99 (3H, s, C(CH_3)$_2$), 1.61 (3H, s, C(CH_3)$_2$), 0.89 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 153.7 (C), 145.4 (C), 142.3 (C), 141.0 (CH), 129.0 (2 x CH), 128.4 (CH), 127.9 (2 x CH), 127.2 (2 x CH), 126.4 (CH), 124.5 (2 x CH), 110.9 (CH), 107.1 (CH), 96.3 (C), 74.8 (C), 70.6 (CH_2), 60.7 (CH), 52.4 (CH), 29.7 (CH_3), 26.8 (CH_2), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{30}NO_4$ $[M+H]^+$: 420.2169, found: 420.2171.

*(4R)-3-[(2R,3R)-2-Benzyl-3-hydroxy-3-(naphthalen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**26**)*
On a 0.50 mmol scale: A solution of the *N*-alkenoyloxazolidine **24d** (154 mg, 0.50 mmol), 2′-acetonaphthone (94 mg, 0.55 mmol) and $Co(acac)_2{\cdot}2H_2O$ (6.4 mg, 0.025 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 6 h. The reaction mixture was filtered through a short plug of SiO_2 using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *aldol product* **26** (218 mg, 91%) as a white solid.
On a 5.00 mmol scale: A solution of the *N*-alkenoyloxazolidine **24d** (1.54 g, 5.00 mmol), 2′-acetonaphthone (936 mg, 5.50 mmol) and $Co(acac)_2{\cdot}2H_2O$ (64 mg, 0.25 mmol) in THF (25 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 10.0 mL, 10.0 mmol) was then added over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 16 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (20 mL), and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *aldol product* **26** (2.16 g, 90%) as a white solid. m.p. 139-141 °C; $[\alpha]_D^{21}$ –374 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3389 (OH), 3026, 1622 (C=O), 1455, 1417, 1377, 1066, 909, 768, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.82-7.76 (2H, m, ArH), 7.82-7.79

(1H, m, Ar*H*) 7.55-7.13 (12H, m, Ar*H*), 7.07 (2H, br s, Ar*H*), 5.53 (1H, s, O*H*), 3.35 (1H, app d, *J* = 8.7 Hz, CH_2O), 3.22-3.09 (2H, m, CH_2O and C*H*C=O), 3.17 (1H, dd, *J* = 8.7, 6.6 Hz, CH_2N), 2.93 (1H, dd, *J* = 11.9, 2.8 Hz, CH_2Ph), 2.52 (1H, dd, *J* = 13.2, 2.8 Hz, CH_2Ph), 1.91 (3H, s, C(CH_3)$_2$), 1.53 (3H, s, C(CH_3)$_2$), 0.87 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 145.0 (C), 142.0 (C), 137.3 (C), 133.2 (C), 132.0 (C), 128.9 (2 x CH), 128.3 (CH), 128.2 (CH), 128.0 (2 x CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 127.1 (2 x CH), 127.0 (CH), 126.5 (CH), 126.4 (CH), 125.6 (CH), 124.5 (2 x CH), 96.1 (C), 75.3 (C), 70.1 (CH_2), 60.5 (CH), 55.6 (CH), 35.1 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{32}H_{34}NO_3$ $[M+H]^+$: 480.2533, found: 480.2532.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for new compounds in Tables 4–5 and eq 2.

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